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(54) Title: NOVEL GENES AND PROTEINS ENCODED THEREBY

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(54) 発明の名称: 新規遺伝子及びそれにコードされる蛋白質

(57) Abstract: Novel genes containing domains encoding proteins are directly cloned from cDNA libraries originating in human adult whole brain, human tonsil, human adult hippocampus and human fetal whole brain. The base sequences and functions thereof are identified. DNAs containing base sequences encoding the following polypeptides (a) and (b): (a) a polypeptide comprising an amino acid sequence which is the same or substantially the same as one of the amino acid sequences represented by SEQ ID NOS: 1 to 31; and (b) a polypeptide comprising an amino acid sequence derived from one of the amino acid sequences represented by SEQ ID NOS: 1 to 31 by deletion, substitution or addition of a part of the amino acids and having substantially the same biological activity; recombinant proteins encoded by the above DNAs; and proteins containing these polypeptides.

[続葉有]



(57) 要約:

ヒト成人全脳、ヒト扁桃、ヒト成人海馬及びヒト胎児全脳由来のcDNAライブラリーから、蛋白質をコードしている領域を含む新規なDNAを直接クローニングし、それらの塩基配列を決定し、更にそれらの機能を同定すること。

以下の(a)又は(b)のポリペプチドをコードする塩基配列を含むDNA:

(a) 配列番号: 1乃至31のいずれか一つで示されるアミノ酸配列と同一又は実質的に同一のアミノ酸配列から成るポリペプチド、

(b) 配列番号: 1乃至31のいずれか一つで示されるアミノ酸配列において、一部のアミノ酸が欠失、置換又は付加されたアミノ酸配列から成り、(a)のポリペプチドの機能と実質的に同質の生物学的活性を有するポリペプチド、上記DNAにコードされる組換えポリペプチド、及び該ポリペプチドを含む蛋白質。

明 細 書

新規遺伝子及びそれにコードされる蛋白質

技術分野

本発明は、DNA及び該DNAを含む遺伝子、並びに該DNAにコードされる組換えポリペプチド及び該ポリペプチドを含む新規組換え蛋白質に関する。

背景技術

ヒトゲノム計画における大規模シーケンシングによって、2001年2月にヒトゲノムドラフト配列が公開された。

ヒトゲノム計画の最終目的は単にゲノム全塩基配列を決定することではなく、その構造情報、即ち、DNAの塩基配列情報からヒトのさまざまな生命現象を読み解くことにあろう。

ヒトゲノム配列中で蛋白質をコードしている領域はそのごく一部であり、現在は、ニューラルネットワークや隠れマルコフモデルと呼ばれる情報科学の手法を用いて、そのコード領域の予測が行われている。しかしながら、それらの予測精度はまだ十分なものではない。

今回、本発明者は新規な遺伝子を見出すべく、ヒト成人全脳、ヒト扁桃、ヒト成人海馬及びヒト胎児全脳由来のcDNAライブラリーから、蛋白質をコードしている領域を含む新規なDNAを直接クローニングすることに成功し、それらの塩基配列を決定して本発明を完成させた。

発明の開示

即ち、本発明は第一の態様として、以下の(a)又は(b)のポリペプチドをコー

ドする塩基配列を含むDNAに係る:

(a) 配列番号: 1乃至31のいずれか一つで示されるアミノ酸配列と同一又は実質的に同一のアミノ酸配列から成るポリペプチド、

(b) 配列番号: 1乃至31のいずれか一つで示されるアミノ酸配列において、一部のアミノ酸が欠失、置換又は付加されたアミノ酸配列から成り、(a)のポリペプチドの機能と実質的に同質の生物学的活性を有するポリペプチド。

本発明の第二の態様として、以下の(a)又は(b)のDNAに係る:

(a) 配列番号: 1乃至31のいずれか一つで示される塩基配列において、夫々の配列で示されるアミノ酸配列をコードする塩基配列を含むDNA、

(b) (a)のDNAとストリンジェントな条件下でハイブリダイズし、(a)のアミノ酸配列から成るポリペプチドの機能と実質的に同質の生物学的活性を有する蛋白質をコードするDNA。

以上の本発明の第一及び第二の態様であるDNAをまとめて、以下、「本発明DNA」ともいう。又、本発明はこれらDNAを含む遺伝子にも係る。

更に、本発明は上記DNA又は遺伝子にコードされる組換えポリペプチド(以下、「本発明ポリペプチド」ともいう。)、及び該ポリペプチドを含む組換え蛋白質に係る。

本発明DNAを有するクローンの名称、本発明ポリペプチド又は蛋白質の長さ、その機能については、表1に示されている。

本発明DNAは、市販されている(クロンテック社製)ヒト成人全脳、ヒト扁桃、ヒト成人海馬及びヒト胎児全脳のmRNAを出発材料として、本発明者が調製したcDNAライブラリーから、cDNA断片として単離した後に、塩基配列を決定し同定したものである。

即ち、具体的には、小原他の方法(DNA Research Vol.4,53-59(1997))に従って調製したヒト成人全脳、ヒト扁桃、ヒト成人海馬及びヒト胎児全脳由来のcDNAライブラリーからクローンをランダムに単離する。

次に、ハイブリダイゼーションにより、重複クローン(繰り返し出てくるクローン)

を除き、その後インビトロでの転写翻訳を行い50kDa以上の産物が認められるクローンについてその両末端の塩基配列を決定する。

更に、こうして得られた末端塩基配列をクエリーとして既知遺伝子のデータベースにて相同性検索を行い、その結果、新規であることが判明したクローンについて全塩基配列を決定する。

また、上記のスクリーニング法に加えて、cDNAの5'および3'の末端配列をヒトのゲノム配列に対応させ、それらが挟む領域に未知の長鎖遺伝子が確認された場合には、そのcDNAの全長解析をおこなう。

このようにして既知の遺伝子に依存した従来のクローニング方法では得られなかった未知の遺伝子も、システムチックにクローニングを行なうことができる。

又、短い断片や得られた配列に人工的な間違いが起こらないように十分な注意を払いながら、RACE等のPCR法を使用することによっても、本発明DNAを含むヒト由来遺伝子の全領域を調製することも可能である。

更に、本発明は、本発明DNA又は本発明DNAを含む遺伝子を含有する組換えベクター、該組換えベクターを保持する形質転換体、該形質転換体を培養し、本発明ポリペプチド若しくは該ポリペプチドを含む組換え蛋白質を生成、蓄積せしめ、これを採取することの特徴とする、本発明ポリペプチド若しくは該ポリペプチドを含む組換え蛋白質、又はその塩の製造方法、及び、こうして得られる本発明ポリペプチド若しくは該ポリペプチドを含む組換え蛋白質又はその塩を提供する。

又、本発明は、本発明DNA又は遺伝子を含有してなる医薬、本発明ポリペプチド若しくはその部分ポリペプチド又は該ポリペプチドを含む組換え蛋白質をコードする塩基配列を含むポリヌクレオチド(DNA)、それら塩基配列に実質的に相補的な塩基配列を有するアンチセンスヌクレオチド、該ポリヌクレオチド又はアンチセンスヌクレオチドを含有してなる医薬、本発明ポリペプチド若しくはその部分ポリペプチド、及び、該ポリペプチド又はそれらを含む組換え蛋白質を含有してなる医薬に係る。

更に、本発明は、本発明ポリペプチド若しくはその部分ポリペプチド又は該ポリペプチドを含む組換え蛋白質又はそれらの塩に対する抗体、及び、本発明ポリペプチド、その部分ポリペプチド若しくは該ポリペプチドを含む組換え蛋白質又はそれらの塩、又はそれらに対する抗体を用いることを特徴とする、それら物質と特異的に相互作用する物質のスクリーニング方法、スクリーニング用キット、並びに、該スクリーニング方法によって同定される物質(化合物)自体等にも係る。

発明を実施する為の最良の形態

本発明DNAとしては、前述した本発明ポリペプチドをコードする塩基配列から成るものであればいかなるものであってもよい。また、ヒトの脳、又は、それ以外の組織、例えば、心臓、肺、肝臓、脾臓、腎臓、精巣、等の細胞・組織に由来するcDNAライブラリー等から同定・単離されたcDNA、又は、合成DNAのいずれでもよい。

ライブラリー作成に使用するベクターは、バクテリオファージ、プラスミド、コスミド、ファージミドなどいずれであってもよい。また、前記した細胞・組織より total RNA画分または mRNA画分を調製したものを用いて、直接 Reverse Transcription coupled Polymerase Chain Reaction(以下、「RT-PCR法」と略称する)によって増幅することもできる。

配列番号:1乃至31のいずれか一つで示されるアミノ酸配列と実質的に同一のアミノ酸配列とは、配列番号:1乃至31のいずれか一つで示される全アミノ酸配列との相同性の程度が、全体の平均で約70%以上、好ましくは約80%以上、更に好ましくは約90%以上、特に好ましくは約95%以上であるアミノ酸配列を意味する。

従って、本発明の配列番号:1乃至31のいずれか一つで示されるアミノ酸配列と実質的に同一のアミノ酸配列から成るポリペプチドとしては、例えば、前記の各配列番号で示されるアミノ酸配列に対して上記の相同性を有し、各配列

番号で示されるアミノ酸配列から成るポリペプチドの機能と実質的に同質の生物学的活性(機能)を有するポリペプチドを挙げることが出来る。ここで、実質的に同質とは、それらの活性(機能)が性質的に同質であることを示す。

又、本発明ポリペプチドには、例えば、配列番号:1乃至31のいずれか一つで示されるアミノ酸配列中の一部(好ましくは、1~20個程度、より好ましくは1~10個程度、さらに好ましくは数個)のアミノ酸が欠失、置換又は付加したアミノ酸配列、或いはそれらを組み合わせたアミノ酸配列から成り、配列番号:1乃至31のいずれか一つで示されるアミノ酸配列から成るポリペプチドの機能と実質的に同質の生物学的活性(機能)を有するポリペプチドも含まれる。

上記の配列番号:1乃至31のいずれか一つで示されるアミノ酸配列と実質的に同一のアミノ酸配列から成るポリペプチド、又はその一部のアミノ酸が欠失、置換又は付加したアミノ酸配列から成るポリペプチドは、例えば、部位特異的変異導入法、遺伝子相同組換え法、プライマー伸長法、及びPCR法等の当業者に周知の方法を適宜組み合わせて、容易に作成することが可能である。

尚、その際に、実質的に同質の生物学的活性を有するためには、当該ポリペプチドを構成するアミノ酸のうち、同族アミノ酸(極性・非極性アミノ酸、疎水性・親水性アミノ酸、陽性・陰性荷電アミノ酸、芳香族アミノ酸など)同士の置換が可能性として考えられる。又、実質的に同質の生物学的活性の維持のためには、本発明の各ポリペプチドに含まれる機能ドメイン内のアミノ酸は保持されることが望ましい。

更に、本発明DNAは、配列番号:1乃至31のいずれか一つで示される塩基配列において、夫々の配列で示されるアミノ酸配列をコードする塩基配列を含むDNA、及び、該DNAとストリンジェントな条件下でハイブリダイズし、各配列で示されるアミノ酸配列から成るポリペプチドの機能と同質の生物学的活性(機能)を有するポリペプチド(蛋白質)をコードするDNAを包含する。

かかる条件下で、配列番号:1乃至31のいずれか一つで示される塩基配列

において、夫々の配列で示されるアミノ酸配列をコードする塩基配列を含むDNAとハイブリダイズできるDNAとしては、例えば、該DNAの全塩基配列との相同性の程度が、全体の平均で約80%以上、好ましくは約90%以上、より好ましくは約95%以上である塩基配列を含有するDNA等を挙げることが出来る。

ハイブリダイゼーションは、カレント・プロトコルズ・イン・モレキュラー・バイオロジー(Current protocols in molecular biology (edited by Frederick M. Ausubel et al., 1987))に記載の方法等、当業界で公知の方法あるいはそれに準じる方法に従って行なうことができる。また、市販のライブラリーを使用する場合、添付の使用説明書に記載の方法に従って行なうことができる。

ここで、「ストリンジェントな条件」とは、例えば、65℃の1mM EDTA ナトリウム、0.5M リン酸水素ナトリウム(pH7.2)、7% SDS 水溶液中でハイブリダイズさせ、65℃の1mM EDTA ナトリウム、40mM リン酸水素ナトリウム(pH7.2)、1% SDS 水溶液中でメンブレンを洗浄する条件でのサザンブロットハイブリダイゼーションで本発明DNAプローブにハイブリダイズする程度の条件である。

本発明DNAのクローニングの手段としては、本発明ポリペプチドの部分等の適当な塩基配列を有する合成DNAプライマーを用いてPCR法によって増幅するか、または適当なベクターに組み込んだDNAを本発明ポリペプチドの一部あるいは全領域をコードするDNA断片もしくは合成DNAを用いて標識したものとハイブリダイゼーションによって選別することができる。

ハイブリダイゼーションの方法は、例えば、上記の Current protocols in molecular biology (edited by Frederick M. Ausubel et al., 1987)に記載の方法などに従って行なうことができる。また、市販のライブラリーを使用する場合、添付の使用説明書に記載の方法に従って行なうことができる。

クローン化されたポリペプチドをコードするDNAは目的によりそのまま、または所望により制限酵素で消化したり、リンカーを付加したりして使用することができる。該DNAはその5'末端側に翻訳開始コドンとしてのATGを有し、また3'末端側には翻訳終止コドンとしてのTAA、TGAまたはTAGを有していてもよい。これらの翻訳開始コドンや翻訳終止コドンは、適当な合成DNAアダプターを用

いて付加することもできる。

本発明の蛋白質の発現ベクターは、当該技術分野で公知の方法に従って作成することが出来る。例えば、(1)本発明DNA又は本発明DNAを含む遺伝子を含有するDNA断片を切り出し、(2)該DNA断片を適当な発現ベクター中のプロモーターの下流に連結することにより製造することができる。

ベクターとしては、大腸菌由来のプラスミド(例、pBR322、pBR325、pUC18、pUC118)、枯草菌由来のプラスミド(例、pUB110、pTP5、pC194)、酵母由来プラスミド(例、pSH19、pSH15)、 λ ファージなどのバクテリオファージ、レトロウイルス、ワクシニアウイルス、パキウイルスなどの動物ウイルス等を利用することが出来る。

本発明で用いられるプロモーターとしては、遺伝子の発現に用いる宿主に対応した適切なプロモーターであればいかなるものでもよい。例えば、宿主が大腸菌である場合は、trpプロモーター、lacプロモーター、recAプロモーター、 λ PLプロモーター、lppプロモーターなどが、宿主が枯草菌である場合は、SPO1プロモーター、SPO2プロモーター、penPプロモーターなど、宿主が酵母である場合は、PHO5プロモーター、PGKプロモーター、GAPプロモーター、ADHプロモーターなどが好ましい。動物細胞を宿主として用いる場合は、SR α プロモーター、SV40プロモーター、LTRプロモーター、CMVプロモーター、HSV-TKプロモーターなどが挙げられる。

発現ベクターには、以上の他に、所望により当該技術分野で公知の、エンハンサー、スプライシングシグナル、ポリA付加シグナル、選択マーカー、SV40複製オリジン等を付加することができる。また、必要に応じて、本発明のDNAにコードされた蛋白質を他の蛋白質(例えば、グルタチオンSトランスフェラーゼ及びプロテインA)との融合蛋白質として発現させることも可能である。このような融合蛋白質は、適当なプロテアーゼを使用して切断し、それぞれの蛋白質に分離することが出来る。

宿主細胞としては、例えば、エシエリヒア属菌、バチルス属菌、酵母、昆虫細胞、昆虫、動物細胞などが用いられる。

エシエリヒア属菌の具体例としては、エシエリヒア・コリ (*Escherichia coli*) K12-DH1 (Proc. Natl. Acad. Sci. USA, 60巻, 160(1968)), JM103 (Nucleic Acids Research, 9巻, 309(1981)), JA221 (Journal of Molecular Biology, 120巻, 517(1978)), 及び HB101 (Journal of Molecular Biology, 41巻, 459(1969)) 等が用いられる。

バチルス属菌としては、例えば、バチルス・サチルス (*Bacillus subtilis*) MI14 (Gene, 24巻, 255(1983)), 207-21 [Journal of Biochemistry, 95巻, 87(1984)] 等が用いられる。

酵母としては、例えば、サッカロマイセス セレビシエ (*Saccaromyces cerevisiae*) AH22, AH22R-, NA87-11A, DKD-5D, 20B-12、シゾ サッカロマイセス ポンベ (*Schizosaccaromyces pombe*) NCYC1913, NCYC 2036、サッカロマイセス ピキア パストリス (*Saccaromyces picjia pastoris*) 等が用いられる。

動物細胞としては、例えば、サル細胞 COS-7, Vero, チャイニーズハムスター細胞 CHO (以下、CHO細胞と略記), dhfr遺伝子欠損 CHO細胞, マウス L細胞, マウス AtT-20, マウスミエローマ細胞, ラット GH3, ヒト FL細胞などが用いられる。

これら宿主細胞の形質転換は、当該技術分野で公知の方法に従って行うことが出来る。例えば、以下に記載の文献を参照することが出来る。

Proc. Natl. Acad. Sci. USA, 69巻, 2110(1972); Gene, 17巻, 107(1982); Molecular & General Genetics, 168巻, 111(1979); Methods in Enzymology, 194巻, 182-187(1991); Proc. Natl. Acad. Sci. USA, 75巻, 1929(1978); 細胞工学別冊8 新 細胞工学実験プロトコル, 263-267(1995) (秀潤社発行); 及び Virology, 52巻, 456(1973)。

このようにして得られた、本発明DNA又は本発明DNAを含む遺伝子を含有

する発現ベクターで形質転換された形質転換体は、当該技術分野で公知の方法に従って培養することが出来る。

例えば、宿主がエシェリヒア属菌の場合、培養は通常約15～43℃で約3～24時間行ない、必要により、通気や攪拌を加えることもできる。宿主がバチルス属菌の場合、培養は通常、約30～40℃で約6～24時間行ない、必要により通気や攪拌を加えることもできる。

宿主が酵母である形質転換体を培養する際、培養は通常、pH約5～8に調整された培地を用いて約20℃～35℃で約24～72時間行ない、必要に応じて通気や攪拌を加えることもできる。

宿主が動物細胞である形質転換体を培養する際、pHは約6～8に調整された培地を用いて、通常約30℃～40℃で約15～60時間行ない、必要に応じて通気や攪拌を加えることもできる。

上記培養物から本発明ポリペプチド又は蛋白質を分離精製するには、例えば、培養後、公知の方法で菌体あるいは細胞を集め、これを適当な緩衝液に懸濁し、超音波、リゾチームおよび／または凍結融解などによって菌体あるいは細胞を破壊したのち、遠心分離やろ過により蛋白質の粗抽出液を得る。緩衝液の中に尿素や塩酸グアニジンなどの蛋白質変性剤や、トリトンX-100TMなどの界面活性剤が含まれていてもよい。培養液中に蛋白質が分泌される場合には、培養終了後、公知の方法で菌体あるいは細胞と上清とを分離し、上清を集める。このようにして得られた培養上清、あるいは抽出液中に含まれる蛋白質の精製は、公知の分離・精製法を適切に組み合わせて行なうことができる。

こうして得られた本発明ポリペプチド(蛋白質)は、公知の方法あるいはそれに準じる方法によって塩に変換することができ、逆に塩で得られた場合には公知の方法あるいはそれに準じる方法により、遊離体または他の塩に変換することができる。更に、組換え体が産生する蛋白質を、精製前または精製後に、トリプシン及びキモトリプシンのような適当な蛋白修飾酵素を作用させることにより、任意に修飾を加えたり、ポリペプチドを部分的に除去することもできる。

本発明ポリペプチド(蛋白質)又はその塩の存在は、様々な結合アッセイ及び特異抗体を用いたエンザイムイムノアッセイ等により測定することができる。

本発明ポリペプチド(蛋白質)は、C末端が通常カルボキシル基($-\text{COOH}$)またはカルボキシレート($-\text{COO}^-$)であるが、C末端がアミド($-\text{CONH}_2$)またはエステル($-\text{COOR}$)であってもよい。ここでエステルにおけるRとしては、例えば、メチル、エチル、 n -プロピル、イソプロピルもしくは n -ブチルなどのC1-6アルキル基、例えば、シクロペンチル、シクロヘキシルなどのC3-8シクロアルキル基、例えば、フェニル、 α -ナフチルなどのC6-12アリール基、例えば、ベンジル、フェネチルなどのフェニル-C1-2アルキル基もしくは α -ナフチルメチルなどの α -ナフチル-C1-2アルキル基などのC7-14アラルキル基のほか、経口用エステルとして汎用されるピバロイルオキシメチルエステルなどが用いられる。

本発明ポリペプチド(蛋白質)がC末端以外にカルボキシル基(またはカルボキシレート)を有している場合、カルボキシル基がアミド化またはエステル化されているものも本発明の蛋白質に含まれる。この場合のエステルとしては、例えば上記したC末端のエステルなどが用いられる。さらに、本発明の蛋白質には、N末端のメチオニン残基のアミノ基が保護基(例えば、ホルミル基、アセチル基などのC1-6アシル基など)で保護されているもの、生体内で切断されて生成するN末端のグルタミン酸残基がピログルタミン化したもの、分子内のアミノ酸の側鎖上にある、例えばOH、COOH、 NH_2 、SHなどが適当な保護基(例えば、ホルミル基、アセチル基などのC1-6アシル基など)で保護されているもの、あるいは糖鎖が結合したいわゆる糖蛋白質などの複合蛋白質なども含まれる。

本発明の蛋白質の部分ポリペプチドとしては、前記した本発明ポリペプチド(蛋白質)の部分ペプチドであって、実質的に同質の活性を有するものであればいずれのものでもよい。例えば、本発明ポリペプチド(蛋白質)の構成アミノ酸配列のうち少なくとも10個以上、好ましくは50個以上、さらに好ましくは70

個以上、最も好ましくは200個以上のアミノ酸配列を有するポリペプチドの機能と実質的に同質の生物学的活性を示すことが用いられる。本発明の部分ポリペプチドとしては、低分子量のもの、中分子量のもの、高分子量のものが好ましい。又、本発明の部分ペプチドはC末端がカルボキシル基(—COOH)またはカルボキシレート(—COO⁻)で終る蛋白質、蛋白質、蛋白質、蛋白質、蛋白質のごとく、C末端がアミド(—CONH₂)またはアミン(—NH₂)でもよい。さらに、本発明の部分ペプチドには、前記のN末端のヒスチジン残基のアミノ基が保護基で、生体内で切断され生成したグルタミル基がピロリジン環の側鎖上の置換基が適当な保護基でもあってもよい。糖鎖が結合したいわゆる糖ペプチドなどの複糖質を含む本発明の部分ペプチドは、例えば、試薬、実験の標的として若しくはその一部として使用することが出来る。

本発明の蛋白質またはその部分ペプチドの塩としては、とりわけ生理的に好ましい。そのような塩としては、例えば、無機酸(塩酸、硫酸)との塩、あるいは有機酸(例えば、酢酸、フマル酸、マレイン酸、コハク酸、酒石酸、クエン酸、安息香酸、メタンスルホン酸、ベンゼンスルホン酸)との塩から。

本発明の蛋白質またはその部分ペプチドもしくはそれらの塩またはそれらの塩を公知の化学合成方法を用いて調製することも出来る。

例、市販の蛋白質合成樹脂を用い、α-アミノ基と側鎖官能基を、目的とする蛋白質の配列通りに、当業界に公知の方法に従い、樹脂上で縮合させる。反応の最後にかき出しと同時に各種保護基を除去し、さらに高希釈

溶液中で分子内ジスルフィド結合形成反応を実施し、目的の蛋白質、その部分ペプチドまたはそれらのアミド体を取得する。上記した保護アミノ酸の縮合に関しては、例えば、DCC、N,N'-ジイソプロピルカルボジイミド、及び N-エチル-N'-(3-ジメチルアミノプロリル)カルボジイミドのようなカルボジイミド類に代表される蛋白質合成に使用できる各種活性化試薬を用いることができる。これらによる活性化にはラセミ化抑制添加剤(例えば、HOBt, HOOBt)とともに保護アミノ酸を直接樹脂に添加するかまたは、対称とする酸無水物または HOBt エステルあるいは HOOBt エステルとしてあらかじめ保護アミノ酸の活性化を行なった後に樹脂に添加することができる。

保護アミノ酸の活性化や樹脂との縮合に用いられる溶媒としては、酸アミド類、ハロゲン化炭化水素類、アルコール類、スルオキシド類、及びエーテル類等、当業界において蛋白質縮合反応に使用しうることが知られている溶媒から適宜選択されうる。反応温度は蛋白質結合形成反応に使用され得ることが知られている範囲から適宜選択される。活性化されたアミノ酸誘導体は通常1.5～4倍過剰で用いられる。ニンヒドリン反応を用いたテストの結果、縮合が不十分な場合には保護基の脱離を行うことなく縮合反応を繰り返すことにより十分な縮合を行なうことができる。反応を繰り返しても十分な縮合が得られないときには、無水酢酸またはアセチルイミダゾールを用いて未反応アミノ酸をアセチル化して、後の反応に影響を及ぼさないようにすることができる。

原料の各アミノ基、カルボキシル基、及びセリン水酸基等の保護基としても、当該技術分野において、通常使用される基を使用することができる。

原料の反応に関与すべきでない官能基の保護ならびに保護基、およびその保護基の脱離、反応に関与する官能基の活性化などは公知の基または公知の手段から適宜選択しうる。

本発明の部分ペプチドまたはそれらの塩は、当該技術分野において自体公知のペプチドの合成法に従って、あるいは本発明の蛋白質を適当なペプチダーゼで切断することによって製造することができる。ペプチドの合成法としては、

例えば、固相合成法、液相合成法のいずれによっても良い。公知の縮合方法や保護基の脱離としては、例えば、以下の(1)～(3)に記載された方法が挙げられる。

(1) 泉屋信夫他、ペプチド合成の基礎と実験、丸善(株) (1975 年)

(2) 矢島治明 および榊原俊平、生化学実験講座 1、蛋白質の化学 IV、205、(1977 年)

(3) 矢島治明監修、続医薬品の開発 第 14 巻 ペプチド合成 広川書店

反応後の精製も自体公知の方法、例えば、溶媒抽出・蒸留・カラムクロマトグラフィー・液体クロマトグラフィー・再結晶などを組み合わせて本発明の部分ペプチドを精製単離することができる。上記方法で得られる部分ペプチドが遊離体である場合は、公知の方法によって適当な塩に変換することができるし、逆に塩で得られた場合は、公知の方法によって遊離体に変換することができる。

本発明ポリペプチド(蛋白質)、その部分ペプチドまたはそれらの塩に対する抗体は、それらを認識し得るものであれば、ポリクローナル抗体、モノクローナル抗体の何れであってもよい。本発明ポリペプチド(蛋白質)、その部分ペプチドまたはそれらの塩に対する抗体は、本発明ポリペプチド(蛋白質)又はその部分ペプチドを抗原として用い、公知の抗体または抗血清の製造法に従って製造することができる。

本発明の抗体は、体液や組織などの被検体中に存在する本発明ポリペプチド(蛋白質)等を検出するために使用することができる。また、これらを精製するために使用する抗体カラムの作製、精製時の各分画中の本発明ポリペプチド(蛋白質)の検出、被検細胞内における本発明ポリペプチド(蛋白質)の挙動の分析などのために使用することができる。

更に、本発明の抗体は、公知の方法による被検液中の本発明ポリペプチド(蛋白質)等の定量、特に、モノクローナル抗体を使用したサンドイッチ免疫測定法による定量、及び組織染色等による検出などに使用することができる。それによって、例えば、本発明ポリペプチド(蛋白質)等が関与する疾病の診断を

行なうことができる。

これらの目的には、抗体分子そのものを用いてもよく、また、抗体分子のF(a b')₂、Fab'、あるいはFab画分を用いてもよい。本発明の抗体を用いる本発明の蛋白質等の定量法は、特に制限されるべきものではなく、被測定液中の抗原量(例えば、蛋白質量)に対応した抗体、抗原もしくは抗体-抗原複合体の量を化学的または物理的手段により検出し、これを既知量の抗原を含む標準液を用いて作製した標準曲線より算出する測定法であれば、いずれの測定法を用いてもよい。例えば、ネフロメトリー、競合法、イムノメトリック法およびサンドイッチ法が好適に用いられるが、感度、特異性の点で、後述するサンドイッチ法を用いるのが好ましい。標識物質を用いる測定法に用いられる標識剤としては、当該技術分野で公知の、例えば、放射性同位元素、酵素、蛍光物質、発光物質などを用いることが出来る。

これらの測定・検出方法に関する一般的な技術手段の詳細については、総説、成書などを参照することができる。例えば、入江 寛編「続ラジオイムノアッセイ」(講談社、昭和54年発行)、石川栄治ら編「酵素免疫測定法」(第3版)(医学書院、昭和62年発行)、「Methods in ENZYMOLOGY」Vol. 70(Immunochemical Techniques(Part A))、同書 Vol. 73(Immunochemical Techniques(Part B))、同書 Vol. 74(Immunochemical Techniques(Part C))、同書 Vol. 84(Immunochemical Techniques(Part D:Selected Immunoassays))、同書 Vol. 92(Immunochemical Techniques(Part E:Monoclonal Antibodies and General Immunoassay Methods))、同書 Vol. 121(Immunochemical Techniques(Part I:Hybridoma Technology and Monoclonal Antibodies))(以上、アカデミックプレス社発行)などを参照することができる。

本発明ポリペプチド(蛋白質)又はその部分ポリペプチドをコードするDNAに実質的に相補的な塩基配列を有するアンチセンスオリゴヌクレオチド(DNA)としては、当該DNAの塩基配列に実質的に相補的な塩基配列を有し、該DNAの発現を抑制し得る作用を有するものであれば、いずれのアンチセンスDNAで

あってもよい。実質的に相補的な塩基配列とは、例えば、本発明DNAに相補的な塩基配列の全塩基配列または部分塩基配列と好ましくは約90%以上、より好ましくは約95%以上、最も好ましくは100%の相同性を有する塩基配列などが挙げられる。又、これらアンチセンスDNAと同様の作用を有する核酸配列(RNAまたはDNAの修飾体)も本発明でいうアンチセンスDNAに含まれる。これらのアンチセンスDNAは、公知のDNA合成装置などを用いて製造することができる。

更に、本発明ポリペプチド(蛋白質)等は、これら物質と特異的に相互作用する化合物をスクリーニングする為の試薬として有用である。すなわち、本発明は、本発明ポリペプチド(蛋白質)、その部分ペプチド若しくはそれらの塩、又はそれらに対する抗体を用いることを特徴とする、該物質又はそれらの塩と特異的に相互作用する化合物のスクリーニング方法、及びその為のスクリーニング用キットを提供する。

本発明のスクリーニング方法またはスクリーニング用キットを用いて同定される化合物またはその塩は、上記した試験化合物から選ばれた化合物であり、本発明ポリペプチド(蛋白質)等と相互作用し、その生物学的活性を調節、阻害、促進、又は拮抗等する化合物である。該化合物またはその塩は、本発明の蛋白質等の活性に直接作用するものであってもよいし、本発明ポリペプチド(蛋白質)等の発現に作用することによって間接的に本発明ポリペプチド(蛋白質)等の活性に作用するものであってもよい。該化合物の塩としては、例えば、薬学的に許容可能な塩などが用いられる。例えば、無機塩基との塩、有機塩基との塩、無機酸との塩、有機酸との塩、塩基性または酸性アミノ酸との塩などがあげられる。本発明ポリペプチド(蛋白質)等の生物学的活性を阻害する化合物も上記各種疾病に対する治療・予防剤などの医薬として使用できる可能性がある。

本発明DNA及び該DNAを含む遺伝子をプローブとして使用することにより、本発明ポリペプチド又はその部分ペプチドをコードするDNAまたはmRNAの異

常(遺伝子異常)を検出することができるので、例えば、該DNAまたはmRNAの損傷、突然変異あるいは発現低下や、該DNAまたはmRNAの増加あるいは発現過多などの遺伝子診断剤として有用である。本発明のDNAを用いる上記の遺伝子診断は、例えば、公知のノーザンハイブリダイゼーションやPCR-SSCP法(Genomics, 第5巻, 874~879頁(1989年)、Proceedings of the National Academy of Sciences of the United States of America, 第86巻, 2766~2770頁(1989年))などにより実施することができる。

更に、本発明DNA又は遺伝子に異常があったり、欠損している場合あるいは発現量が減少している場合、生体内において正常な機能を発揮できない患者に対しては、公知手段に従って(1)レトロウイルスベクター、アデノウイルスベクター、アデノウイルスアソシエーテッドウイルスベクターなどの適当なベクターをベヒクルとして使用する遺伝子治療によって、本発明DNA又は遺伝子を該患者体内に導入し、発現させるか、又は(2)本発明の蛋白質等を該患者に注入すること等によって、該患者において本発明の蛋白質等の機能を発揮させることができるものと考えられる。

本発明DNA又は遺伝子を、該DNAを単独、又は、摂取促進のための補助剤とともに、遺伝子銃やハイドロゲルカテーテルのようなカテーテルによって投与することも可能である。

本明細書および表において、塩基やアミノ酸などを略号で表示する場合、IU PAC-IUB Commision on Biochemical Nomenclature による略号あるいは当該分野における慣用略号に基づくものであり、またアミノ酸に関し光学異性体があり得る場合は、特に明示しなければL体を示すものとする。

実施例

以下に、実施例により本発明をさらに具体的に説明するが、本発明はそれに限定されるものではない。なお、実施例における各種遺伝子操作は、上記の Current protocols in molecular biology (edited by Frederick M. Ausubel et al., 1987)に記載されている方法に従った。

(1) ヒト成人全脳、ヒト扁桃、ヒト成人海馬及びヒト胎児全脳由来cDNAライブラリーの構築

NotI部位を有するオリゴヌクレオチド(GACTAGTTCTAGATCGCGAGCG GCCGCCC(T)₁₅)(インビトロジェン)をプライマーとして、ヒト成人全脳、ヒト扁桃、ヒト成人海馬及びヒト胎児全脳由来mRNA(クローンテック社製)を鋳型に SuperScriptII 逆転写酵素キット(インビトロジェン社製)で2本鎖cDNAを合成した。SalI部位を有するアダプター(インビトロジェン社製)をcDNAとライゲーションした。その後、NotI消化し、1%濃度の低融解アガロース電気泳動により、3kb以上のDNA断片を精製した。

精製cDNA断片を、SalI-NotI制限酵素処理した pBluescript IISK+ プラスミドとライゲーションした。大腸菌 ElectroMax DH10B 株(インビトロジェン)にエレクトロポレーション法によりこの組換えプラスミドを導入した。

(2) スクリーニング(その1)

次いで、こうして構築したcDNAライブラリーからランダムにクローンをピックアップし、メンブランにスポッティングした。次に、これまでに本発明者等によって既に全長の解析が行われている約 1,300 個のクローンの塩基配列に基づき作成したオリゴDNA(各21塩基)の混合物の各3'末端をターミナルトランスフェラーゼでDIGラベルし、これらをプローブとして使用してドットハイブリダイゼーション(Current protocols in molecular biology(edited by Frederick M. Ausubel et al., 1987))により、重複クローン(繰り返し出てくるクローン)を除いた。

次に、インビトロでの転写翻訳(プロメガ社 TNT T7 Quick Coupled Transcription/Translation System cat.no.L1107)を行い、50kDa以上の産物が認められるクローンを選択した。

次に、選択したクローンの末端塩基配列を決定し、得られた配列をクエリーとして相同検索プログラム BLASTN 2.2.1 (Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schaffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation

of protein databas search programs", Nucleic Acids Res. 25:3389-3402)を用いて、nr(All GenBank+EMBL+DDBJ+PDB sequences (but no EST, STS, GSS, or phase 0, 1 or 2 HTGS sequences))データベースに対して相同検索を行った。その結果、相同遺伝子が存在しなかったもの、即ち、新規遺伝子であるものについて全塩基配列を決定した。

スクリーニング(その2)

cDNA の 5'および 3'の末端配列を、相同検索プログラム BLASTN2.2.1 を用いて、ヒトのゲノム配列(に対応させた)。

次に、それらが挟むゲノム領域から、Genscan プログラム(Burge, C. and Karlin, S. 1997, Prediction of complete gene structures in human genomic DNA, *J Mol. Biol.*, 268, 78-94、ゲノムから遺伝子を予測するコンピューターソフト)を用いて、コードされる遺伝子を抜き出した。これをクエリーとして、相同検索プログラム BLASTN2.1.3 を用いて、mergedb(かずさ DNA 研究所で決定したヒトの cDNA の配列と GenBank の homo sapiens データベースから EST とゲノムを除いたものを重複なく混ぜ合わせた、かずさ DNA 研究所で独自に作成した DNA 配列データベース)に対応させ、新規の長鎖(Genscan 予想 cds が 1200 bp 以上)遺伝子が確認された場合には、5'および 3'の末端配列決定をおこなった cDNA の全長解析をおこなった。

配列決定には、PEアプライドバイオシステム社製の DNA シークエンサー (ABI PRISM377) と同社製反応キットを使用した。大部分の配列はショットガンクローンをダイターミネーター法を用いて決定した。一部の塩基配列については、決定した塩基配列を元にしてオリゴヌクレオチドを合成し、プライマーウォーキング法で決定した。

このようにして新規 DNA 又は遺伝子のスクリーニングを行なった。その結果、配列表の配列番号 1 乃至 31 のいずれか一つに示された新規 DNA 又は遺伝子が検出された。

これらの新規 DNA 又は遺伝子について、上記の配列決定方法によりその塩

基配列を決定した。本発明DNA又は遺伝子を有するクローンの名称は表1に示されている。

(3) 本発明DNAの相同性検索

次に、こうして得られた全塩基配列に基づき、クローンのアミノ酸配列を既知配列ライブラリーnr に対して解析プログラム BLASTP 2.2.1 (Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schaffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402)を用いて検索したところ、表2に示した各相同遺伝子と相同性を示すことが明らかになった。尚、表2には、これら相同遺伝子に関する情報、即ち、その名称、データベースID、生物種、蛋白質長、及び記載文献が挙げられている。又、これら各表中の「生物種」の略号の意味は表3で説明されている。

更に、各クローンに含まれる本発明DNA又は遺伝子と表2に示した各相同遺伝子との相同性に関する各種データを表4にまとめた。これら表中の各項目の意味は以下の通りである。

「相同領域 クローン」クローンの相同領域の起点及び終点

「相同領域 相同遺伝子」相同遺伝子の相同領域の起点及び終点

「Score」この値が高いほど信頼度が高い

「E-value」この値が0に近いほど信頼度が高い

「相同性」相同領域のアミノ酸残基の一致の割合

「相同範囲率」相同遺伝子中の相同領域の割合

(4) 各種ドメインの検索

次に、クローンに含まれるDNAがコードするアミノ酸配列中から、Pfam 6.6 に含まれる検索ツール Pfam HMM ver 2.1 Search (HMMPFAM) (Sonnhammer ELL, Eddy SR, Birney E, Bateman A, Durbin R (1998) Pfam: multiple sequenc

alignments and HMM-profiles of protein domains, Nucleic Acids Research 26:320-322)を用いて機能ドメインを検索した。

更に、膜蛋白予測プログラムである SOSUI system (ver. 1.0 / 10, Mar., 1996) (Takatsugu Hirokawa, Seah Boon-Chieng and Shigeki Mitaku, SOSUI: Classification and Secondary Structure Prediction System for Membrane Proteins, Bioinformatics (formerly CABIOS) 1998 May;14(4):378-379.) を用いて膜貫通ドメインを検索した。

これらの検出された機能ドメイン及び膜貫通ドメインを表5にそれぞれのクローンについて示した。

これら表中の各項目の意味は以下の通りである。

「機能ドメイン」Pfam SOSUI により検出されたドメイン

「クローン from」クローン機能ドメインの起点

「クローン to」クローン機能ドメインの終点

「相同遺伝子 from」相同遺伝子機能ドメインの起点

「相同遺伝子 to」相同遺伝子機能ドメインの終点

「Score(Pfam のみ)」この値が高いほど信頼度が高い

「Exp(Pfam のみ)」この値が 0 に近いほど信頼度が高い

又、各機能ドメインの完全標記は以下の通りである。

ank: Ankyrin repeats;

ArfGap: ADP-ribosylation-factor GTPase-activating protein;

DSPc: Dual specificity phosphatase, catalytic domain;

PH: PH domain;

Rhodanese: Rhodanese-like domain;

RhoGAP: GTPase activator proteins towards Rho/Rac/Cdc42-like small GTPases;

Sema: semaphorins

Zf-C2H2: Zinc finger, C2H2 type.

(5) 発現部位

RT-PCR Coupled ELISA を用いて、組織と脳の部位での発現を、それぞれで一番強い発現を示したものを表 6 に示した。尚、組織及び脳の部位の完全標記を表 7 に示した。

(6) 染色体位置

クローンの DNA 配列を、相同検索プログラム BLASTN 2.2.1 を用いてヒトゲノムをコードするクローンのライブラリー(に対応させた。対応したクローンの説明 (Definition)の中からこのクローンが由来した染色体の番号を抽出し、これを表 6 に示した。

以上の、相同性、相同性遺伝子に関する情報、各種ドメイン、発現部位、及び染色体位置、等に基づき、当業者であれば、本発明の DNA 又は遺伝子が表 1 に示した各機能を有するものと予測することが出来る。

尚、以下のクローンに含まれる遺伝子が完全長であることは、以下の理由により判定した。

fj15353: 相同遺伝子とのアラインメントから相同遺伝子の全体を含んでいると考えられる。ただし、タンパク質の N 末端付近(配列番 13 のアミノ酸配列 1 から 12)の相同性はない。

hj05518: 相同遺伝子とのアラインメントから相同遺伝子の全体を含んでいると考えられる。ただし、タンパク質の C 末端付近(配列番号 20 のアミノ酸配列 318 から 362)の相同性はない。

pj00464: 相同遺伝子とのアラインメントから相同遺伝子の全体を含んでいると考えられる。ただし、タンパク質の N 末端付近(配列番号 30 のアミノ酸配列 1 から 85)の相同性はない。

表 1

配列 番号	クローン			
	名称	蛋白質 長	完全長ま たは部分 配列	予測される機能
1	fg00690	712	-	-
2	fg00806	136	-	-
3	fg04185	85	-	-
4	fg05002	112	-	-
5	fg06117	1311	-	-
6	fh10218	91	-	-
7	fh10993	1191	-	-
8	fh23414	902	-	-
9	fh23774	775	-	-
10	fh26241	653	-	-
11	fj05607	855	-	-
12	fj08520	802	-	-
13	fj15353	665	完全長	リン酸化チロシン残基、リン酸化セリン残基、リン酸化スレオニン残基を脱リン酸化する。細胞周期や細胞シグナル伝達系の一つであるMAPキナーゼカスケードにおいて働く
14	fj15966	530	-	-
15	hg00527	127	-	-
16	hg02500	179	-	-
17	hg03328	114	-	-
18	hg03458	76	-	-
19	hh04042	108	-	-
20	hj05518	362	完全長	E1B 19kDaあるいは、Bcl-2と相互作用し細胞死を抑制する
21	hj06603	804	-	-
22	pf00208	420	-	-
23	pf00674	1497	部分配列	Rasに結合し、シグナルを核への伝達
24	pf00943	400	-	-
25	pg00954	1020	-	-
26	pg01135	787	-	-
27	ph00175	1516	-	-
28	ph00321	509	-	-
29	pj00125	400	-	-
30	pj00464	886	完全長	マウスのセマフォリン4Cとの相同性から、ヒトマウスのセマフォリン4Cの全長を含むと考えられる。神経細胞の軸索の誘導シグナルとして働き、軸索の伸長阻害作用をすると考えられる。
31	pj01678	893	部分配列	セマフォリンファミリーの一つと考えられる。神経細胞の軸索の誘導シグナルとして働き、軸索の伸長阻害作用をすると考えられる。

表 2

配 列 番 号	相同遺伝子				
	名称	データベースID	生物 種	蛋白質 長	文献
1	KIAA0940	ref NP_055727.1	Hs	684	-
5	R29381_1	gb AAC08316.1	Hs	757	-
7	hypothetical protein	emb CAB61359.1	Hs	1033	-
9	hypothetical protein	gi 9506679	Hs	637	-
10	similar to KIAA0904	gb AAD54514.1 A C006023_1	Hs	727	-
11	melt gene product	gb AAF50606.1	Dm	992	-
12	unnamed protein product	dbj BAA91770.1	Hs	1084	-
13	dual specificity phosphatase & protein-tyrosine phosphatase	gi 4758212	Hs	625	J. Neurochem. 65 (4), 1823-1833 (1995)
20	BCL2/adenovirus E1B 19kD- interacting protein 2	gi 4757856	Hs	314	Cell 79 (2), 341-351 (1994)
21	centaurin beta2	emb CAB41450.1	Hs	778	-
23	GAP-associated protein p190	pir A38218	Rn	1493	Cell 69 (3), 539-549 (1992)
24	CG10355	gb AAF53821.1	Dm	550	-
26	hypothetical protein	dbj BAB12129.1	Mf	390	-
28	dJ257A7.1	emb CAA15504.1	Hs	118	-
30	SEMAPHORIN 4C PRECURSOR (SEMAPHORIN D)	sp Q64151 SM4C_ MOUSE	Mm	834	FEBS Lett. 370 (3), 269-272 (1995)
31	SEMAPHORIN 4B (SEMAPHORIN C)	sp Q62179 SM4B_ MOUSE	Mm	782	Neuron 14 (5), 941- 948 (1995)

表 3

略記	英語名	日本名
Bt	<i>Bos taurus</i>	ウシ
Ce	<i>Caenorhabditis elegans</i>	センチュウ
Cr	<i>Chlamydomonas reinhardtii</i>	クラミドモナス
Dm	<i>Drosophila melanogaster</i>	ショウジョウバエ
Dr	<i>Danio rerio</i>	ゼブラフィッシュ
Gg	<i>Gallus gallus</i>	ニワトリ
Hs	<i>Homo sapiens</i>	ヒト
Mf	<i>Macaca fascicularis</i>	カニクイザル
Mm	<i>Mus musculus</i>	マウス
Oc	<i>Oryctolagus cuniculus</i>	ウサギ
Pa	<i>Pseudomonas aeruginosa</i>	シュードモナス
Rn	<i>Rattus norvegicus</i>	ラット
Tg	<i>Tripneustes gratilla</i>	ウニ
Tr	<i>Takifugu rubripes</i>	フグ
Vc	<i>Volvox carteri f. nagariensis</i>	ヴォルボックス
Xl	<i>Xenopus laevis</i>	アフリカツメガエル

表 4

配 列 番 号	相同領域				相同値			
	クローン		相同遺伝子		Score	E-value	相同性	相同範囲率
	from	to	from	to				
1	70	712	1	684	755	0	59%(419/709)	100%
2	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-
5	1	388	315	709	760	0	97%(387/395)	52%
6	-	-	-	-	-	-	-	-
7	241	1154	1	923	1762	0	96%(892/923)	89%
8	-	-	-	-	-	-	-	-
9	29	476	1	448	936	0	99%(447/448)	70%
10	1	653	75	727	1337	0	99%(649/653)	90%
11	23	338	1	316	253	5e-66	43%(137/317)	32%
12	1	798	348	1084	1390	0	90%(726/798)	68%
13	13	665	14	625	500	e-140	45%(305/665)	98%
14	-	-	-	-	-	-	-	-
15	-	-	-	-	-	-	-	-
16	-	-	-	-	-	-	-	-
17	-	-	-	-	-	-	-	-
18	-	-	-	-	-	-	-	-
19	-	-	-	-	-	-	-	-
20	1	317	1	302	356	3e-97	54%(176/321)	96%
21	18	778	17	746	867	0	59%(452/761)	94%
22	-	-	-	-	-	-	-	-
23	48	1485	50	1484	2723	0	93%(1357/1456)	96%
24	18	316	3	307	282	4e-75	45%(140/305)	55%
25	-	-	-	-	-	-	-	-
26	398	787	1	390	799	0	100%(390/390)	100%
27	-	-	-	-	-	-	-	-
28	205	322	1	118	251	1e-65	100%(118/118)	100%
29	-	-	-	-	-	-	-	-
30	86	886	33	834	1474	0	87%(698/802)	96%
31	111	893	1	782	1385	0	84%(664/784)	100%

表 5

配列番号	クローン						相同遺伝子					
	機能ドメイン	From	To	Score	Exp		機能ドメイン	From	To	Score	Exp	
3	sosui	48	70	-	-							
11	PH	739	841	65.1	7.8e-17							
13	Rhodanese DSPc	11 158	131 297	53.4 244.5	4.9e-12 1.4e-69		DSPc	160	299	248.9	7.2e-71	
15	sosui	18	40	-	-							
	sosui	66	88	-	-							
16	sosui	1	23	-	-							
17	sosui	3	25	-	-							
	sosui	54	76	-	-							
21	PH ArfGap ank ank	272 406 672 705	366 528 704 737	67.2 212 33.1 16.5	2.1e-17 8.7e-60 6.3e-06 0.63		PH ArfGap	267 399	361 520	66.4 232	3.4e-17 8.4e-66	
23	RhoGAP	1260	1411	178.5	1.1e-49		RhoGAP	1242	1393	157.7	1.9e-43	
24	sosui	58	80	-	-		sosui	465	487	-	-	
	sosui	99	121	-	-							
	sosui	138	160	-	-							
	sosui	163	185	-	-							
	sosui	195	217	-	-							
	sosui	236	257	-	-							
	sosui	269	291	-	-							
	sosui	305	327	-	-							
	sosui	341	363	-	-							
25	zf-C2H2 zf-C2H2 zf-C2H2 zf-C2H2	81 108 136 982	103 130 159 1004	13.8 17.3 18.1 17.2	4 0.36 0.2 0.4							
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表 6

配列 番号	発現部位		染色体位置
	組織	脳	
1	Brain	B.cerebellum	5
2	Testis	B.subthalamicnucleus	22
3	-	-	22
4	Brain	B.cerebellum	22
5	Testis	B.corpuscallosum	19
6	Kidney	B.hippocampus	22
7	Brain	B.cerebellum	7
8	Brain	B.cerebellum	4
9	Ovary	B.substania nigra	5
10	Ovary	B.cerebellum	7
11	Kidney	B.cerebellum	-
12	Testis	B.cerebellum	-
13	Brain	B.cerebellum	12
14	Brain	B.amygdala	6
15	Lung	Spinalcord	22
16	Ovary	B.cerebellum	22
17	-	-	22
18	Ovary	Spinalcord	22
19	Ovary	B.cerebellum	22
20	Brain	B.amygdala	19
21	Brain	Spinalcord	1
22	Liver	B.thalamus	4
23	Brain	-	19
24	Liver	B.amygdala	-
25	Ovary	B.cerebellum	-
26	-	-	-
27	Ovary	B.substania nigra	11
28	Brain	B.caudatenucleus	6
29	S.muscle	B.cerebellum	14
30	Brain	B.substania nigra	2
31	Liver	B.subthalamicnucleus	15

表 7

	標記	日本語
組織	Brain	脳
	Heart	心臓
	Kidney	腎臓
	Liver	肝臓
	Lung	肺臓
	Ovary	卵巣
	Pancreas	膵臓
	S.muscle	骨格筋
	Spleen	脾臓
	Testis	精巣
脳	B.amygdala	脳の扁桃体
	B.caudatenucleus	脳の尾状核
	B.cerebellum	脳の小脳
	B.corpuscallosum	脳の脳梁
	B.hippocampus	脳の海馬
	B.substania nigra	脳の黒質
	B.subthalamice nucleus	脳の視床下部の核
	B.thalamus	脳の視床
	Spinal cord	脊髄

産業上の利用分野

本発明で得られた新規なDNA又は遺伝子を所謂DNAチップ等を集積させ、これに、例えば、精神病等の脳が関与する疾患の患者と対照としての正常人の血液又は組織等から作成したプローブをハイブリダイゼーションさせることによって、これら疾患の診断、治療等に役立てることが出来る。

又、本発明のDNA若しくは遺伝子又はそれらの一部の塩基配列に基づき作成した合成DNAプライマーを使用し、ヒトの血液又は組織から抽出した染色体DNAを用いてPCRを行い、その産物の塩基配列を決定することにより、本発明のDNA又は遺伝子中にある個体によって異なる一塩基の変異、即ち、cSNPsを見出すことが出来る。これにより、個体の体質等が予測され、各自に適した医薬の開発等が可能となる。

又、クロスハイブリダイゼーションにより、マウス等のモデル生物における本発明のDNA又は遺伝子に対するオルソログ(ホモログ、カウンターパート)遺伝子を単離し、例えば、これら遺伝子をノックアウトすることによってヒトの疾患モデル動物を作成し、ヒトの病因となる遺伝子を探索・同定することも可能である。

更に、本発明ポリペプチド、その部分ポリペプチド若しくは該ポリペプチドを含む組換え蛋白質、又は、本発明のDNA又は遺伝子に対する抗体を網羅的に作成し、それらを集積させて所謂PROTEINチップを作成し、患者と正常人との蛋白質発現量の差異を検出する等のプロテオーム解析から、病気の診断・治療等に役立てることが出来る。

請求の範囲

1. 以下の(a)又は(b)のポリペプチドをコードする塩基配列を含むDNA:
(a) 配列番号: 1乃至31のいずれか一つで示されるアミノ酸配列と同一又は実質的に同一のアミノ酸配列から成るポリペプチド、
(b) 配列番号: 1乃至31のいずれか一つで示されるアミノ酸配列において、一部のアミノ酸が欠失、置換又は付加されたアミノ酸配列から成り、(a)のポリペプチドの機能と実質的に同質の生物学的活性を有するポリペプチド。
2. 以下の(a)又は(b)のDNA:
(a) 配列番号: 1乃至31のいずれか一つで示される塩基配列において、夫々の配列で示されるアミノ酸配列をコードする塩基配列を含むDNA、
(b) (a)のDNAとストリンジェントな条件下でハイブリダイズし、(a)のアミノ酸配列から成るポリペプチドの機能と実質的に同質の生物学的活性を有する蛋白質をコードするDNA。
3. 請求項1又は2記載のヒトDNAを含む遺伝子。
4. 以下の(a)又は(b)の組換えポリペプチド:
(a) 配列番号: 1乃至31のいずれか一つで示されるアミノ酸配列と同一又は実質的に同一のアミノ酸配列から成るポリペプチド、
(b) 配列番号: 1乃至31のいずれか一つで示されるアミノ酸配列において、一部のアミノ酸が欠失、置換又は付加されたアミノ酸配列から成り、(a)のポリペプチドの機能と実質的に同質の生物学的活性を有するポリペプチド。
5. 請求項3に記載の遺伝子にコードされる組換え蛋白質。

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SEQUENCE LISTING

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<120> Novel Gene and Proteins Encoded Thereby

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<150> JP 2000-389742

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ggg atg ccg gag ctc agg cat ccc aga cag gag gaa gtg tgt act cac 1123
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acc agc cag gag gaa aca agc ctg cct ggg agg aca gac gat cag ccc 1171
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35

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 Val Lys Glu Tyr Pro Gly Gly Val Arg Ser Met Thr His Leu Pro Gly

60

65

70

acc agc acc tgg ggc tgc cag gca gcc acc cct gca gct gtg ttg aca 1315

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 105 110

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15

acg ccc act aag ggc cca gag ggc aag gtg gcc ggc ccc gcc gac gcc 97

Thr Pro Thr Lys Gly Pro Glu Gly Lys Val Ala Gly Pro Ala Asp Ala

20

25

30

ccc atg gac tct ggt gct gag gaa gag aag gcg gga gca gcc acc gtg 145

Pro Met Asp Ser Gly Ala Glu Glu Glu Lys Ala Gly Ala Ala Thr Val

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35	40	45	
aag aag ccg tct ccc tcc aaa gcc cgc aag aag aag cta aac aag aag			193
Lys Lys Pro Ser Pro Ser Lys Ala Arg Lys Lys Lys Leu Asn Lys Lys			
50	55	60	
ggg agg aag atg gct ggc cgc aag cgc ggg cgc ccc aag aag atg aac			241
Gly Arg Lys Met Ala Gly Arg Lys Arg Gly Arg Pro Lys Lys Met Asn			
65	70	75	80
act gcg aac ccc gag cgg aag ccc aag aag aac caa act gca ctg gat			289
Thr Ala Asn Pro Glu Arg Lys Pro Lys Lys Asn Gln Thr Ala Leu Asp			
85	90	95	
gcc ctg cac gct cag acc gtg tct cag acg gcg gcc tcc tca ccc cag			337
Ala Leu His Ala Gln Thr Val Ser Gln Thr Ala Ala Ser Ser Pro Gln			
100	105	110	
gat gcc tac aga tcc cct cac agc ccg ttc tac cag cta cct ccg agc			385
Asp Ala Tyr Arg Ser Pro His Ser Pro Phe Tyr Gln Leu Pro Pro Ser			
115	120	125	
gtg cag cgg cac tcc ccc aac ccg ctg ctg gtg gcg ccc acc ccg ccc			433
Val Gln Arg His Ser Pro Asn Pro Leu Leu Val Ala Pro Thr Pro Pro			
130	135	140	
gcg ctg cag aag ctt cta gag tcc ttc aag atc cag tac ctg cag ttc			481
Ala Leu Gln Lys Leu Leu Glu Ser Phe Lys Ile Gln Tyr Leu Gln Phe			
145	150	155	160
ctg gca tac aca aag acc ccc cag tac aag gcc agc ctg cag gag ctg			529
Leu Ala Tyr Thr Lys Thr Pro Gln Tyr Lys Ala Ser Leu Gln Glu Leu			
165	170	175	
ctg ggc cag gag aag gag aag aac gcc cag ctc ctg ggt gcg gct cag			577
Leu Gly Gln Glu Lys Glu Lys Asn Ala Gln Leu Leu Gly Ala Ala Gln			

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180	185	190	
cag ctc ctc agc cac tgc cag gcc cag aag gag gag atc agg agg ctg			625
Gln Leu Leu Ser His Cys Gln Ala Gln Lys Glu Glu Ile Arg Arg Leu			
195	200	205	
ttt cag caa aaa ttg gat gag ctg ggt gtg aag gcg ctg acc tac aac			673
Phe Gln Gln Lys Leu Asp Glu Leu Gly Val Lys Ala Leu Thr Tyr Asn			
210	215	220	
gac ctg att caa gcg cag aag gag atc tcc gcc cat aac cag cag ctg			721
Asp Leu Ile Gln Ala Gln Lys Glu Ile Ser Ala His Asn Gln Gln Leu			
225	230	235	240
cgg gag cag tcg gag cag ctg gag cag gac aac cgc gcg ctc cgc ggc			769
Arg Glu Gln Ser Glu Gln Leu Glu Gln Asp Asn Arg Ala Leu Arg Gly			
245	250	255	
cag agc ttg cag ctg ctc aag gct cgc tgc gag gag ctg cag ctg gac			817
Gln Ser Leu Gln Leu Leu Lys Ala Arg Cys Glu Glu Leu Gln Leu Asp			
260	265	270	
tgg gcc acg ctg tcg ctg gag aag ctg ttg aag gag aag cag gcc ctg			865
Trp Ala Thr Leu Ser Leu Glu Lys Leu Leu Lys Glu Lys Gln Ala Leu			
275	280	285	
aag agc cag atc tcg gag aag cag agg cac tgc ctg gag ctg cag atc			913
Lys Ser Gln Ile Ser Glu Lys Gln Arg His Cys Leu Glu Leu Gln Ile			
290	295	300	
agc att gtg gag cta gag aag agc cag cgg cag cag gag ctc ctg cag			961
Ser Ile Val Glu Leu Glu Lys Ser Gln Arg Gln Gln Glu Leu Leu Gln			
305	310	315	320
ctc aag tcc tgt gtg ccg cct gac gac gcc ctg tcc ctg cac ctg cgt			1009
Leu Lys Ser Cys Val Pro Pro Asp Asp Ala Leu Ser Leu His Leu Arg			

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325	330	335	
ggg aag ggc gcc ctg ggc cgc gag ctg gag cct gac gcc agc cgg ctg			1057
Gly Lys Gly Ala Leu Gly Arg Glu Leu Glu Pro Asp Ala Ser Arg Leu			
340	345	350	
cac ctg gag ctg gac tgc acc aag ttc tcg ctg cct cac ttg agc agc			1105
His Leu Glu Leu Asp Cys Thr Lys Phe Ser Leu Pro His Leu Ser Ser			
355	360	365	
atg agc cgc gag ctc tcc atg aac ggc cag gct gct ggc tat gag ctc			1153
Met Ser Pro Glu Leu Ser Met Asn Gly Gln Ala Ala Gly Tyr Glu Leu			
370	375	380	
tgc ggt gtg ctg agc cgg cct tcg tcg aag cag aac acg ccc cag tac			1201
Cys Gly Val Leu Ser Arg Pro Ser Ser Lys Gln Asn Thr Pro Gln Tyr			
385	390	395	400
ctg gcc tca ccc ctg gac cag gag gtg gtg ccc tgt acc cct agc cac			1249
Leu Ala Ser Pro Leu Asp Gln Glu Val Val Pro Cys Thr Pro Ser His			
405	410	415	
gtc ggc cgg ccg cgc ctg gag aag ctg tct ggc cta gcc gca ccc gac			1297
Val Gly Arg Pro Arg Leu Glu Lys Leu Ser Gly Leu Ala Ala Pro Asp			
420	425	430	
tac act agg ctg tcc ccg gcc aag att gtg ctg agg cgg cac ctg agc			1345
Tyr Thr Arg Leu Ser Pro Ala Lys Ile Val Leu Arg Arg His Leu Ser			
435	440	445	
cag gac cac acg gtg ccc ggc agg ccg gct gcc agt gag ctg cat tcg			1393
Gln Asp His Thr Val Pro Gly Arg Pro Ala Ala Ser Glu Leu His Ser			
450	455	460	
aga gct gag cac acc aag gag aac ggc ctt ccc tac cag agc ccc agc			1441
Arg Ala Glu His Thr Lys Glu Asn Gly Leu Pro Tyr Gln Ser Pro Ser			

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465	470	475	480	
gtg cct ggc agc atg aag ctg agc cct cag gac ccg cgg ccc ctg tcc				1489
Val Pro Gly Ser Met Lys Leu Ser Pro Gln Asp Pro Arg Pro Leu Ser				
	485	490	495	
cct ggg gcc ttg cag ctt gct gga gag aag agc agt gag aag ggc ctg				1537
Pro Gly Ala Leu Gln Leu Ala Gly Glu Lys Ser Ser Glu Lys Gly Leu				
	500	505	510	
aga gag cgc gcc tac ggc agc agc ggg gag ctc atc acc agc ctg ccc				1585
Arg Glu Arg Ala Tyr Gly Ser Ser Gly Glu Leu Ile Thr Ser Leu Pro				
	515	520	525	
atc agc atc ccg ctc agc acc gtg cag ccc aac aag ctc ccg gtc agc				1633
Ile Ser Ile Pro Leu Ser Thr Val Gln Pro Asn Lys Leu Pro Val Ser				
	530	535	540	
att ccc ctg gcc agc gtg gtg ctg ccc agc cgc gcc gag agg gcg agg				1681
Ile Pro Leu Ala Ser Val Val Leu Pro Ser Arg Ala Glu Arg Ala Arg				
545	550	555	560	
agc acc ccc agt ccc gtg ctg cag ccc cgt gac ccc tcg tcc aca ctt				1729
Ser Thr Pro Ser Pro Val Leu Gln Pro Arg Asp Pro Ser Ser Thr Leu				
	565	570	575	
gaa aag cag att ggt gct aat gcc cac ggt gct ggg agc aga agc ctt				1777
Glu Lys Gln Ile Gly Ala Asn Ala His Gly Ala Gly Ser Arg Ser Leu				
	580	585	590	
gcc ctg gcc ccc gca ggc ttc tcc tac gct ggc tcg gtg gcc atc agc				1825
Ala Leu Ala Pro Ala Gly Phe Ser Tyr Ala Gly Ser Val Ala Ile Ser				
	595	600	605	
ggg gcc ttg gcg ggc agc ccg gcc tct ctc aca cct gga gcc gag ccg				1873
Gly Ala Leu Ala Gly Ser Pro Ala Ser Leu Thr Pro Gly Ala Glu Pro				

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610	615	620	
gcc acc ttg gat gag tcc tcc agc tct ggg agc ctt ttt gcc acc gtg	1921		
Ala Thr Leu Asp Glu Ser Ser Ser Ser Gly Ser Leu Phe Ala Thr Val			
625	630	635	640
ggg tcc cgc agc tcc acg cca cag cac ccc ctg ctg ctg gca cag ccc	1969		
Gly Ser Arg Ser Ser Thr Pro Gln His Pro Leu Leu Leu Ala Gln Pro			
645	650	655	
cgg aac tcg ctt cct gcc tct ccc gcc cac cag ctc tcc tcc agt ccc	2017		
Arg Asn Ser Leu Pro Ala Ser Pro Ala His Gln Leu Ser Ser Ser Pro			
660	665	670	
cgg ctt ggt ggg gcc gcc cag ggc cgg ttg ccc gag gcc agc aag gga	2065		
Arg Leu Gly Gly Ala Ala Gln Gly Pro Leu Pro Glu Ala Ser Lys Gly			
675	680	685	
gac ctg ccc tcc gat tcc ggc ttc tca gat cct gag agt gaa gcc aag	2113		
Asp Leu Pro Ser Asp Ser Gly Phe Ser Asp Pro Glu Ser Glu Ala Lys			
690	695	700	
agg agg att gtg ttc acc atc acc act ggt gcg ggc agt gcc aag cag	2161		
Arg Arg Ile Val Phe Thr Ile Thr Thr Gly Ala Gly Ser Ala Lys Gln			
705	710	715	720
tcg ccc tcc agc aag cac agc ccc ctg acc gcc agc gcc cgt ggg gac	2209		
Ser Pro Ser Ser Lys His Ser Pro Leu Thr Ala Ser Ala Arg Gly Asp			
725	730	735	
tgt gtg ccg agc cac ggg cag gac agt cgc agg cgc ggc cgg cgg aag	2257		
Cys Val Pro Ser His Gly Gln Asp Ser Arg Arg Arg Gly Arg Arg Lys			
740	745	750	
cga gca tct gcg ggg acg ccc agc ttg agc gca ggc gtg tcc ccc aag	2305		
Arg Ala Ser Ala Gly Thr Pro Ser Leu Ser Ala Gly Val Ser Pro Lys			

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760 760 760 760 76

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 Arg Arg euSd Ala. Ala. Ala. Ala Gly Leu Phe Gb il;
 770 5 ; ; ;

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 Ser Pro bnAs Met Met Met Met Val Ser Asr An le
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 850 5 ; ; ;

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 Glu Asn lyLe Gly Gly Gly Gly Arg Lys Pro Pn il
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cca gtc gcag aag: aag: aag: aag tcc acc ttc cc ga73
 Pro Val erLy Lys Lys Lys Lys Ser Thr Phe P ls

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Ile Gly Leu Ala Lys Ser Ala Asp Ser Pro Leu Gln Ala Ser Ser Ala			
915	920	925	
ctc agc cag aac tcc ctg ttc acg ttc cgg ccc gcc ctg gag gag ccc			2833
Leu Ser Gln Asn Ser Leu Phe Thr Phe Arg Pro Ala Leu Glu Glu Pro			
930	935	940	
tct gcc gat gcc aag ctg gcc gct cac ccc agg aaa ggc ttt ccc ggc			2881
Ser Ala Asp Ala Lys Leu Ala Ala His Pro Arg Lys Gly Phe Pro Gly			
945	950	955	960
tcc ctg tcg ggg gct gac gga ctc agc ccg ggc acc aac cct gcc aac			2929
Ser Leu Ser Gly Ala Asp Gly Leu Ser Pro Gly Thr Asn Pro Ala Asn			
965	970	975	
ggc tgc acc ttc ggc ggg ggc ctg gcc gcg gac ctg agt tta cac agc			2977
Gly Cys Thr Phe Gly Gly Gly Leu Ala Ala Asp Leu Ser Leu His Ser			
980	985	990	
ttc agt gat ggt gct tct ctt ccc cac aag ggc ccc gag gcg gcc ggc			3025
Phe Ser Asp Gly Ala Ser Leu Pro His Lys Gly Pro Glu Ala Ala Gly			
995	1000	1005	
ctg agc tcc ccg ctg agt ttc ccc tcg cag cgc ggc aag gag ggc tcg			3073
Leu Ser Ser Pro Leu Ser Phe Pro Ser Gln Arg Gly Lys Glu Gly Ser			
1010	1015	1020	
gac gcc aac cct ttc ctg agc aag agg cag ctg gac ggc ctg gct ggg			3121
Asp Ala Asn Pro Phe Leu Ser Lys Arg Gln Leu Asp Gly Leu Ala Gly			
1025	1030	1035	1040
ctg aag ggc gag ggc agc cgc agc aag gag gca ggg gag ggc ggc cta			3169
Leu Lys Gly Glu Gly Ser Arg Ser Lys Glu Ala Gly Glu Gly Gly Leu			

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1045	1050	1055	
ccg ctg tgc ggg ccc acg gac aag acc cca ctg ctg agc ggc aag gcc	3217		
Pro Leu Cys Gly Pro Thr Asp Lys Thr Pro Leu Leu Ser Gly Lys Ala			
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gcc aag gcc cgg gac cgc gag gtc gac ctc aag aat ggc cac aac ctc	3265		
Ala Lys Ala Arg Asp Arg Glu Val Asp Leu Lys Asn Gly His Asn Leu			
1075	1080	1085	
ttc atc tct gcg gcg gcc gtg cct ccc gga agc ctc ctc agc ggc ccc	3313		
Phe Ile Ser Ala Ala Ala Val Pro Pro Gly Ser Leu Leu Ser Gly Pro			
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ggc ctg gcc ccg gcg gcg tcc tcc gca ggc ggc gcg gcg tcc tcc gcc	3361		
Gly Leu Ala Pro Ala Ala Ser Ser Ala Gly Gly Ala Ala Ser Ser Ala			
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Gln Thr His Arg Ser Phe Leu Gly Pro Phe Pro Pro Gly Pro Gln Phe			
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Ala Leu Gly Pro Met Ser Leu Gln Ala Asn Leu Gly Ser Val Ala Gly			
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Ser Ser Val Leu Gln Ser Leu Phe Ser Ser Val Pro Ala Ala Ala Gly			
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ctg gtg cac gtg tcg tcc gct gcc acc aga ctg acc aac tcg cac gcc	3553		
Leu Val His Val Ser Ser Ala Ala Thr Arg Leu Thr Asn Ser His Ala			
1170	1175	1180	
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Met Gly Ser Phe Ser Gly Val Ala Gly Gly Thr Val Gly Gly Arg Gln			

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1185	1190	1195	1200	
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Pro Leu Gln Val Pro Phe Arg Thr Leu Leu Gln Gln Glu Leu Ser Cys				
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Arg Ser Pro Gly Ala Gly Arg Pro Pro Pro Ser Val His Gly Gly Glu				
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Leu Gln Ser Cys Gly Glu Arg Ala His Ala Glu Ser Val Cys Leu Gly				
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Cys Gly Arg Pro Gly Ser Gly Lys Ala Leu Gly Ala Gly Val Gly				
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90

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10

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 20 25 30 35

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70

75

80

ctc tca gga ccc aca gtg acc act cta ggc tcc tat gag gct tcc gag 1544

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His Leu Ala Gln Ala Glu Ile Gln Ser Leu Arg Gln Ala Ala Glu Asp	
260 265 270 275	
tcc gca act gaa cat gag agt gac ata gca tcc ctg cag gag gat ctc	2120
Ser Ala Thr Glu His Glu Ser Asp Ile Ala Ser Leu Gln Glu Asp Leu	
280 285 290	
tgc cgg atg cag aat gaa ctt gaa gac atg gaa cgc att cgg gga gat	2168
Cys Arg Met Gln Asn Glu Leu Glu Asp Met Glu Arg Ile Arg Gly Asp	
295 300 305	
tat gag atg gag atc gcc tcc ctc cgt gca gaa atg gaa atg aag agc	2216
Tyr Glu Met Glu Ile Ala Ser Leu Arg Ala Glu Met Glu Met Lys Ser	
310 315 320	
tct gaa cca tcc ggt agt tta ggt ctc tca gat tac tct ggg tta caa	2264
Ser Glu Pro Ser Gly Ser Leu Gly Leu Ser Asp Tyr Ser Gly Leu Gln	
325 330 335	
gaa gaa ctg cag gag ctg cgg gaa cgc tac cat ttc ctg aat gag gaa	2312
Glu Glu Leu Gln Glu Leu Arg Glu Arg Tyr His Phe Leu Asn Glu Glu	
340 345 350 355	
tac cgg gcc ctg cag gag agc aac agc agc ctc acg ggg cag ctt gca	2360
Tyr Arg Ala Leu Gln Glu Ser Asn Ser Ser Leu Thr Gly Gln Leu Ala	
360 365 370	
gat ctg gag agt gag agg aca cag aga gca aca gag aga tgg ctg cag	2408

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Asp Leu Glu Ser Glu Arg Thr Gln Arg Ala Thr Glu Arg Trp Leu Gln	
375	380 385
tcc caa aca ctg agt atg acg tca gca gag tct cag act tca gaa atg	2456
Ser Gln Thr Leu Ser Met Thr Ser Ala Glu Ser Gln Thr Ser Glu Met	
390	395 400
gat ttc tta gag cct gat cct gaa atg cag ttg tta cgg cag cag cta	2504
Asp Phe Leu Glu Pro Asp Pro Glu Met Gln Leu Leu Arg Gln Gln Leu	
405	410 415
cgg gat gct gaa gag cag atg cat ggc atg aag aac aag tgt cag gaa	2552
Arg Asp Ala Glu Glu Gln Met His Gly Met Lys Asn Lys Cys Gln Glu	
420	425 430 435
ttg tgt tgt gag ttg gaa gag cta cag cat cat cgc cag gtc agt gag	2600
Leu Cys Cys Glu Leu Glu Glu Leu Gln His His Arg Gln Val Ser Glu	
440	445 450
gag gag cag agg cgg ctg cag agg gag ctc aag tgt gct cag aat gag	2648
Glu Glu Gln Arg Arg Leu Gln Arg Glu Leu Lys Cys Ala Gln Asn Glu	
455	460 465
gtg ctt cgg ttt cag acc tcc cac agt gtc acc cag aat gag gag ctg	2696
Val Leu Arg Phe Gln Thr Ser His Ser Val Thr Gln Asn Glu Glu Leu	
470	475 480
aag tcc aga ctc tgt acc ctg cag aaa aaa tat gat act agc cag gat	2744
Lys Ser Arg Leu Cys Thr Leu Gln Lys Lys Tyr Asp Thr Ser Gln Asp	
485	490 495
gag cag aac gag ctc ttg aag atg cag ctg caa ctt cag act gag ctc	2792
Glu Gln Asn Glu Leu Leu Lys Met Gln Leu Gln Leu Gln Thr Glu Leu	
500	505 510 515
cgg cag ctc aaa gtc atg aaa tcc aca ctt gta gaa aac cag agt gag	2840

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Arg Gln Leu Lys Val Met Lys Ser Thr Leu Val Glu Asn Gln Ser Glu	
520 525 530	
aag gag tta ctg tgc cgg ctg cag aag ctg cac ctc cag cac cag aac	2888
Lys Glu Leu Leu Cys Arg Leu Gln Lys Leu His Leu Gln His Gln Asn	
535 540 545	
gtc aca tgt gag aag gaa aag ctg ctg gaa cgg cag cag cag ctg cag	2936
Val Thr Cys Glu Lys Glu Lys Leu Leu Glu Arg Gln Gln Gln Leu Gln	
550 555 560	
gag gag ctg cag tgc cat gag gca gag ctg cag cac ctc agg gat acg	2984
Glu Glu Leu Gln Cys His Glu Ala Glu Leu Gln His Leu Arg Asp Thr	
565 570 575	
gtg gcc tcc ttc aaa gag agc aat gag aag gac aca gag acg cac gct	3032
Val Ala Ser Phe Lys Glu Ser Asn Glu Lys Asp Thr Glu Thr His Ala	
580 585 590 595	
cag ctt cag gag atg aag cag ctg tac cag gcc agc aag gac gag ctg	3080
Gln Leu Gln Glu Met Lys Gln Leu Tyr Gln Ala Ser Lys Asp Glu Leu	
600 605 610	
gag cgg cag aag cac atg tat gac cag ctg gag cag gac ctc ctg ctc	3128
Glu Arg Gln Lys His Met Tyr Asp Gln Leu Glu Gln Asp Leu Leu Leu	
615 620 625	
tgc cag ctg gag ctg aaa gag ctc aag gcc tcc cac ccc att ccg gag	3176
Cys Gln Leu Glu Leu Lys Glu Leu Lys Ala Ser His Pro Ile Pro Glu	
630 635 640	
gac aaa gga aag tgt gct aat aag tgt gac aca ctg ctg tcc aga ctg	3224
Asp Lys Gly Lys Cys Ala Asn Lys Cys Asp Thr Leu Leu Ser Arg Leu	
645 650 655	
aca gaa ttg cag gaa aag tac aag gcc agc cag aag gag atg ggg cag	3272

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Thr Glu Leu Gln Glu Lys Tyr Lys Ala Ser Gln Lys Glu Met Gly Gln	
660	675
ctg cag atg gag cag tgt gag ctc ctg gag gat cag agg agg atg cag	3320
Leu Gln Met Glu Gln Cys Glu Leu Leu Glu Asp Gln Arg Arg Met Gln	
680	690
gag gag cag ggc cag ctg cag gaa gag ctg cac agg ctc aca ctg cca	3368
Glu Glu Gln Gly Gln Leu Gln Glu Glu Leu His Arg Leu Thr Leu Pro	
695	705
ctg cca aag agt ggc ctc tta ctc aag agt cag gag cta ctc acc aag	3416
Leu Pro Lys Ser Gly Leu Leu Leu Lys Ser Gln Glu Leu Leu Thr Lys	
710	720
tta gaa gac ctg tgt gag ctg cag ctg ctc tac caa ggc atg cag gag	3464
Leu Glu Asp Leu Cys Glu Leu Gln Leu Leu Tyr Gln Gly Met Gln Glu	
725	735
gaa cag aag aag ctg ata cag aac caa gac tgt gta tta aaa gaa caa	3512
Glu Gln Lys Lys Leu Ile Gln Asn Gln Asp Cys Val Leu Lys Glu Gln	
740	755
tta gag atc cac gaa gag ctg cga cgt ttc aaa gag tct cat ttc cag	3560
Leu Glu Ile His Glu Glu Leu Arg Arg Phe Lys Glu Ser His Phe Gln	
760	770
gaa gtg ttg gag aat ccc gat gat tcc aaa ttg gct aag tcc tcc aaa	3608
Glu Val Leu Glu Asn Pro Asp Asp Ser Lys Leu Ala Lys Ser Ser Lys	
775	785
tgt aat cga aac aag caa tcc aag ctg ctc atg gag cag atg cag gcc	3656
Cys Asn Arg Asn Lys Gln Ser Lys Leu Leu Met Glu Gln Met Gln Ala	
790	800
ctg cag gtg atg tat gac gcc ggt cag gcg aag cag gag ctc ttg cag	3704

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Leu Gln Val Met Tyr Asp Ala Gly Gln Ala Lys Gln Glu Leu Leu Gln
 805 810 815

caa gag caa ggg agg ctc cta gag gag cgg aag agg ctg cag gca gac 3752
 Gln Glu Gln Gly Arg Leu Leu Glu Glu Arg Lys Arg Leu Gln Ala Asp
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 Leu Gln Leu Cys Leu Glu Glu Met Gln Leu Leu Gln Val Gln Ser Pro
 840 845 850

tct ata aaa atg agc ctt gag tcc tac ggg aag agc tat ggt agc atg 3848
 Ser Ile Lys Met Ser Leu Glu Ser Tyr Gly Lys Ser Tyr Gly Ser Met
 855 860 865

gtc ccc agc aat gag aac tgt cgc aag act tat gat acc act gtg gat 3896
 Val Pro Ser Asn Glu Asn Cys Arg Lys Thr Tyr Asp Thr Thr Val Asp
 870 875 880

gac aat gag agc tat tac aag agt tac acc agc acc cag acc agc agc 3944
 Asp Asn Glu Ser Tyr Tyr Lys Ser Tyr Thr Ser Thr Gln Thr Ser Ser
 885 890 895

aag agc ttt ctc aag agc tat gac agc agc acc agt gcc agt gag gcc 3992
 Lys Ser Phe Leu Lys Ser Tyr Asp Ser Ser Thr Ser Ala Ser Glu Ala
 900 905 910 915

tat ggg aag agt tac tgc act acc agc aac agc agc att acc tat aag 4040
 Tyr Gly Lys Ser Tyr Cys Thr Thr Ser Asn Ser Ser Ile Thr Tyr Lys
 920 925 930

aag agt tac ggc agc acc agt agc tct gac acc tgc cag aag agt ttt 4088
 Lys Ser Tyr Gly Ser Thr Ser Ser Ser Asp Thr Cys Gln Lys Ser Phe
 935 940 945

gtc agc agc tgc act gac gag gaa cct gct gag cct gaa gac atg gag 4136

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Val Ser Ser Cys Thr Asp Glu Glu Pro Ala Glu Pro Glu Asp Met Glu
 950 955 960

cgc ttt gag gaa atg gtt gtg aaa gtg ctg atc aag ctg cag gcg gtg 4184
 Arg Phe Glu Glu Met Val Val Lys Val Leu Ile Lys Leu Gln Ala Val
 965 970 975

cag gcc atg tac cag ata agc cag gag gaa cac agc cag ctg caa gag 4232
 Gln Ala Met Tyr Gln Ile Ser Gln Glu Glu His Ser Gln Leu Gln Glu
 980 985 990 995

cag atg gaa aag tta ctg gcc aag cag aaa gac ctg aag gaa gag ctg 4280
 Gln Met Glu Lys Leu Leu Ala Lys Gln Lys Asp Leu Lys Glu Glu Leu
 1000 1005 1010

gat gcc tgt gaa agg gag ttc aag gag tgc atg gaa tgc ctt gaa aag 4328
 Asp Ala Cys Glu Arg Glu Phe Lys Glu Cys Met Glu Cys Leu Glu Lys
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ccc atg gcc ccc cag aac gac aag aat gag atc aaa gaa ctg cag acc 4376
 Pro Met Ala Pro Gln Asn Asp Lys Asn Glu Ile Lys Glu Leu Gln Thr
 1030 1035 1040

aag ctg cgg gag ctg cag ctg caa tac cag gct agc atg gat gag cag 4424
 Lys Leu Arg Glu Leu Gln Leu Gln Tyr Gln Ala Ser Met Asp Glu Gln
 1045 1050 1055

ggg cgg ctt ctg gta gtg cag gag cag ctg gag ggg cag ctg cag tgc 4472
 Gly Arg Leu Leu Val Val Gln Glu Gln Leu Glu Gly Gln Leu Gln Cys
 1060 1065 1070 1075

tgc cag gag gag ctc cgc cag ctc agg gag aag agg cct tct gtt gtc 4520
 Cys Gln Glu Glu Leu Arg Gln Leu Arg Glu Lys Arg Pro Ser Val Val
 1080 1085 1090

aaa gaa gcc cgg ggg aag aat gct aat aag aac atg aac aag aat gcc 4568

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Lys Glu Ala Arg Gly Lys Asn Ala Asn Lys Asn Met Asn Lys Asn Ala
 1095 1100 1105

aat ggg gtt aaa atg aaa aag gtg acc aag cca tgc tcg gat act tct 4616
 Asn Gly Val Lys Met Lys Lys Val Thr Lys Pro Cys Ser Asp Thr Ser
 1110 1115 1120

gag agc gac ctt gag acc aga aag aag atc agg agg aaa atg aag agg 4664
 Glu Ser Asp Leu Glu Thr Arg Lys Lys Ile Arg Arg Lys Met Lys Arg
 1125 1130 1135

aca aag agg aag agg aga agg aag aag aca gtg aag agg agg agg atg 4712
 Thr Lys Arg Lys Arg Arg Arg Lys Lys Thr Val Lys Arg Arg Arg Met
 1140 1145 1150 1155

acg ccg act ctt ccc ttg aaa gtc ccg aag aaa ata acc ccc tca gac 4760
 Thr Pro Thr Leu Pro Leu Lys Val Pro Lys Lys Ile Thr Pro Ser Asp
 1160 1165 1170

ttt ccg aga gca aaa agt cat ccc cta ccc cca atc ccc cca tct tct 4808
 Phe Pro Arg Ala Lys Ser His Pro Leu Pro Pro Ile Pro Pro Ser Ser
 1175 1180 1185

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 Pro Cys Leu Leu
 1190

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 ggagcccaac agccgagaag gggaggaggagg gcagaggagg gggaccagga aggacacccc 180
 cgtgccccga agacataaat ccctgagtgc ccgggaggag ccttaacaag cgcacggagc 240
 cctcaaggct gcaaagttgg ctttcacagt gcaagccttt ga ttc cca atg ggg 294
 Phe Pro Met Gly

1

gac tca gga tca aga cga tct acc ctg gtc tcc cgg ttg cca ata ttc 342
 Asp Ser Gly Ser Arg Arg Ser Thr Leu Val Ser Arg Leu Pro Ile Phe
 5 10 15 20

aga aga agt att aac aga aga cat gat tct ctt cct tct tca cct tct 390
 Arg Arg Ser Ile Asn Arg Arg His Asp Ser Leu Pro Ser Ser Pro Ser
 25 30 35

tcc agt aat aca gtt ggt gtc cac agt tcc tct cct tcc agc act aac 438
 Ser Ser Asn Thr Val Gly Val His Ser Ser Ser Pro Ser Ser Thr Asn
 40 45 50

tca agc tca ggt agc aca ggt aaa cgg agg agc ata ttc cgt act cct 486
 Ser Ser Ser Gly Ser Thr Gly Lys Arg Arg Ser Ile Phe Arg Thr Pro
 55 60 65

tcc att agc ttc cac cat aag aag ggg agt gag cct aag caa gag cct 534
 Ser Ile Ser Phe His His Lys Lys Gly Ser Glu Pro Lys Gln Glu Pro
 70 75 80

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acc aac cag aac ctt agt att tca aat ggt gct caa cct ggt cac agc 582
 Thr Asn Gln Asn Leu Ser Ile Ser Asn Gly Ala Gln Pro Gly His Ser
 85 90 95 100

aat atg cag aaa ctg agt ttg gaa gaa cat att aag acc agg gga aga 630
 Asn Met Gln Lys Leu Ser Leu Glu Glu His Ile Lys Thr Arg Gly Arg
 105 110 115

cat tct gtt ggt ttt agt agt tca cga aat aag aag ata aca aga tct 678
 His Ser Val Gly Phe Ser Ser Ser Arg Asn Lys Lys Ile Thr Arg Ser
 120 125 130

ttg aca gag gat ttt gaa agg gaa aaa gag cac tca act aac aag aat 726
 Leu Thr Glu Asp Phe Glu Arg Glu Lys Glu His Ser Thr Asn Lys Asn
 135 140 145

gtc ttt ata aat tgt cta agt tct ggc aaa agt gaa ggg gat gat tct 774
 Val Phe Ile Asn Cys Leu Ser Ser Gly Lys Ser Glu Gly Asp Asp Ser
 150 155 160

ggc ttc aca gaa gac caa act cgt cgt tct gtt aag cag tca aca agg 822
 Gly Phe Thr Glu Asp Gln Thr Arg Arg Ser Val Lys Gln Ser Thr Arg
 165 170 175 180

aag cta ctc cct aaa tct ttt tca tct cac tat aaa ttt tct aag cca 870
 Lys Leu Leu Pro Lys Ser Phe Ser Ser His Tyr Lys Phe Ser Lys Pro
 185 190 195

gtt cta cag agc caa tcc att tca ttg gta caa cag tct gaa ttc tca 918
 Val Leu Gln Ser Gln Ser Ile Ser Leu Val Gln Gln Ser Glu Phe Ser
 200 205 210

ttg gaa gtt aca cag tac caa gag aga gaa cct gta tta gta aga gct 966
 Leu Glu Val Thr Gln Tyr Gln Glu Arg Glu Pro Val Leu Val Arg Ala
 215 220 225

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tcg cca tcc tgt tct gtg gat gta aca gaa cgg gca gga agc tct tta 1014
 Ser Pro Ser Cys Ser Val Asp Val Thr Glu Arg Ala Gly Ser Ser Leu
 230 235 240

caa tct cct ttg ctt tct gct gat ctt acc aca gct cag aca cct tca 1062
 Gln Ser Pro Leu Leu Ser Ala Asp Leu Thr Thr Ala Gln Thr Pro Ser
 245 250 255 260

gaa ttt tta gcc ttg act gaa gat tct gtg tct gaa atg gat gca ttt 1110
 Glu Phe Leu Ala Leu Thr Glu Asp Ser Val Ser Glu Met Asp Ala Phe
 265 270 275

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 Ser Lys Ser Gly Ser Met Ala Ser His Cys Asp Asn Phe Gly His Asn
 280 285 290

gat tct acc tct cag atg tcc ctc aat tct gct gct gtt aca aag aca 1206
 Asp Ser Thr Ser Gln Met Ser Leu Asn Ser Ala Ala Val Thr Lys Thr
 295 300 305

aca aca gaa ctt acg gga act gtt ccc tgt gca att atg tct cct ggg 1254
 Thr Thr Glu Leu Thr Gly Thr Val Pro Cys Ala Ile Met Ser Pro Gly
 310 315 320

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 Lys Tyr Arg Leu Glu Gly Gln Cys Ser Thr Glu Ser Asn Ser Leu Pro
 325 330 335 340

gaa acc tct gct gct aat cag aag gaa gtg tta tta caa att gct gaa 1350
 Glu Thr Ser Ala Ala Asn Gln Lys Glu Val Leu Leu Gln Ile Ala Glu
 345 350 355

cta cct gct aca agt gtg agc cac tca gag agt aac cta cca gca gat 1398
 Leu Pro Ala Thr Ser Val Ser His Ser Glu Ser Asn Leu Pro Ala Asp
 360 365 370

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agt gaa aga gaa gaa aat ata ggg tta caa aat ggt gaa aca atg ctg 1446
 Ser Glu Arg Glu Glu Asn Ile Gly Leu Gln Asn Gly Glu Thr Met Leu
 375 380 385

ggg aca aac tcc cca agg aaa ctt gga ttt tat gag caa cat aaa gca 1494
 Gly Thr Asn Ser Pro Arg Lys Leu Gly Phe Tyr Glu Gln His Lys Ala
 390 395 400

ata gcg gaa cat gta aaa ggg atc cat cct att tca gat tca aag ata 1542
 Ile Ala Glu His Val Lys Gly Ile His Pro Ile Ser Asp Ser Lys Ile
 405 410 415 420

ata cct act tct ggt gat cat cat att ttt aac aaa aca tca cat gga 1590
 Ile Pro Thr Ser Gly Asp His His Ile Phe Asn Lys Thr Ser His Gly
 425 430 435

tat gaa gca aat cct gcc aaa gtt ctt gcc agt agt ctc agt cca ttt 1638
 Tyr Glu Ala Asn Pro Ala Lys Val Leu Ala Ser Ser Leu Ser Pro Phe
 440 445 450

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 Arg Glu Gly Arg Phe Ile Glu Arg Arg Leu Arg Ser Ser Ser Glu Gly
 455 460 465

act gca ggg agt agc aga atg att ttg aaa ccg aaa gat gga aat ata 1734
 Thr Ala Gly Ser Ser Arg Met Ile Leu Lys Pro Lys Asp Gly Asn Ile
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 Lys Met Asn Ser Leu Asp Val Leu Asn Asn Leu Gly Ser Cys Glu Leu
 505 510 515

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gat gaa gat gat cta atg ctt gat ctt gaa ttt tta gag gaa cag agt 1878
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 535 540 545

tgt gcc gca gta gtt ctt act cct atg gaa cca atg ata gaa atg aag 1974
 Cys Ala Ala Val Val Leu Thr Pro Met Glu Pro Met Ile Glu Met Lys
 550 555 560

aaa aga gaa gaa cca gaa ttt cct gag cct tcc aaa cag aat ctt tcc 2022
 Lys Arg Glu Glu Pro Glu Phe Pro Glu Pro Ser Lys Gln Asn Leu Ser
 565 570 575 580

ctg aaa tta aca aag gac gtt gat caa gaa gcc agg tgt tcc cac atc 2070
 Leu Lys Leu Thr Lys Asp Val Asp Gln Glu Ala Arg Cys Ser His Ile
 585 590 595

agc cga atg ccc aac agt cca tct gcg gat tgg cct cta caa ggt gtg 2118
 Ser Arg Met Pro Asn Ser Pro Ser Ala Asp Trp Pro Leu Gln Gly Val
 600 605 610

gaa gaa aac gga ggc ata gat tct ctg cca ttc aga ctg atg tta cag 2166
 Glu Glu Asn Gly Gly Ile Asp Ser Leu Pro Phe Arg Leu Met Leu Gln
 615 620 625

gac tgc acg gca gtc aag acg tta tta tta aag atg aag aga gtt ctt 2214
 Asp Cys Thr Ala Val Lys Thr Leu Leu Leu Lys Met Lys Arg Val Leu
 630 635 640

caa gag agt gca gac atg agt cca gca agc agt acc acg tca ctt cct 2262
 Gln Glu Ser Ala Asp Met Ser Pro Ala Ser Ser Thr Thr Ser Leu Pro
 645 650 655 660

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gtt agt cct ctt act gaa gag cca gtg cct ttc aag gat ata atg aaa 2310
 Val Ser Pro Leu Thr Glu Glu Pro Val Pro Phe Lys Asp Ile Met Lys
 665 670 675

gat gaa tgc tgc atg ctc aag ctg cag ctg aaa gag aag gat gaa ctc 2358
 Asp Glu Cys Ser Met Leu Lys Leu Gln Leu Lys Glu Lys Asp Glu Leu
 680 685 690

att tcc caa ctt cag gaa gag ctg gga aaa gtc cgg cat tta cag aag 2406
 Ile Ser Gln Leu Gln Glu Glu Leu Gly Lys Val Arg His Leu Gln Lys
 695 700 705

gct ttt gct tca aga gta gat aaa tcc aca cag act gaa cta cta tgc 2454
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 710 715 720

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 Tyr Asp Gly Leu Asn Leu Lys Arg Leu Glu Thr Val Gln Gly Gly Arg
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 745 750 755

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 Asp Arg Lys Ala Ile His Thr Pro Thr Glu Asp Arg Phe Arg Tyr Ser
 760 765 770

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 Ala Ala Asp Gln Thr Ser Pro Tyr Lys Asn Lys Thr Cys Gln Leu Pro
 775 780 785

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 Ser Leu Cys Leu Ser Asn Phe Leu Lys Asp Lys Glu Leu Ala Glu Val
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 Ile Lys His Ser Arg Gly Thr Tyr Glu Thr Leu Thr Ser Asp Val Thr
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 Gln Asn Leu Arg Ala Thr Val Gly Gln Ser Ser Leu Lys Pro Thr Ala
 825 830 835

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 840 845 850

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 Ala Thr Ala Arg Gln His Ser Thr Phe Thr Gly Arg Phe Gly Gln Pro
 855 860 865

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 Pro Arg Gly Pro Ile Ser Leu His Met Tyr Ser Arg Lys Asn Val Phe
 870 875 880

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 Leu His His Asn Leu His Ser Thr Glu Leu Gln Thr Leu Gly Gln Gln
 885 890 895 900

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61/201

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62/201

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 260 265 270

gct gga att ttg gca aca ggt gaa aaa cag aca gat cca tca aca cca 3142
 Ala Gly Ile Leu Ala Thr Gly Glu Lys Gln Thr Asp Pro Ser Thr Pro
 275 280 285

caa cag gag tct tcg aaa ccg ttg gga gga att cag cct tct tct cag 3190
 Gln Gln Glu Ser Ser Lys Pro Leu Gly Gly Ile Gln Pro Ser Ser Gln
 290 295 300 305

acc atc cag cct aaa gtg gag act gat gct gcc cag gcg gct gtg cag 3238
 Thr Ile Gln Pro Lys Val Glu Thr Asp Ala Ala Gln Ala Ala Val Gln
 310 315 320

agt gca ttt gca gtt ctg ttg act cag tta ata aag gct cag cag tca 3286
 Ser Ala Phe Ala Val Leu Leu Thr Gln Leu Ile Lys Ala Gln Gln Ser
 325 330 335

aag cag aaa gat gtg cta cta gaa gag agg gaa aat gga tcg gga cat 3334
 Lys Gln Lys Asp Val Leu Leu Glu Glu Arg Glu Asn Gly Ser Gly His
 340 345 350

63/201

gaa gcg tca tta caa ctc agg cca cct cca gaa cct agc act ccg gtg 3382
 Glu Ala Ser Leu Gln Leu Arg Pro Pro Pro Glu Pro Ser Thr Pro Val
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tcg gga caa gat gac ctc atc cag cat caa gat atg agg atc ttg gag 3430
 Ser Gly Gln Asp Asp Leu Ile Gln His Gln Asp Met Arg Ile Leu Glu
 370 375 380 385

cta acg cca gaa cca gac cgg cct cga att ctg cct cct gac caa cga 3478
 Leu Thr Pro Glu Pro Asp Arg Pro Arg Ile Leu Pro Pro Asp Gln Arg
 390 395 400

cct ccc gag cct cct gaa cca cca cca gtc act gag gaa gat cta gat 3526
 Pro Pro Glu Pro Pro Glu Pro Pro Pro Val Thr Glu Glu Asp Leu Asp
 405 410 415

tat cgg aca gaa aac cag cat gta ccc acc acc agt tct tca tta act 3574
 Tyr Arg Thr Glu Asn Gln His Val Pro Thr Thr Ser Ser Ser Leu Thr
 420 425 430

gac cct cat gcc gga gtg aag gca gcc ctg tta cag ctg ctt gct cag 3622
 Asp Pro His Ala Gly Val Lys Ala Ala Leu Leu Gln Leu Leu Ala Gln
 435 440 445

cat cag ccc cag gat gac ccc aaa aga gaa ggt ggg att gat tat caa 3670
 His Gln Pro Gln Asp Asp Pro Lys Arg Glu Gly Gly Ile Asp Tyr Gln
 450 455 460 465

gca gga gac act tac gtg tcc act tca gac tac aag gac aac ttt gga 3718
 Ala Gly Asp Thr Tyr Val Ser Thr Ser Asp Tyr Lys Asp Asn Phe Gly
 470 475 480

tcc tct tct ttc tct tct gct cct tat gtt agc aat gat ggt cta gga 3766
 Ser Ser Ser Phe Ser Ser Ala Pro Tyr Val Ser Asn Asp Gly Leu Gly
 485 490 495

64/201

agc agt tct gct cca cca cta gaa cga cgt agt ttc att gga aat tca 3814
 Ser Ser Ser Ala Pro Pro Leu Glu Arg Arg Ser Phe Ile Gly Asn Ser
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 Asp Ile Gln Ser Leu Asp Asn Tyr Ser Thr Ala Ser Ser His Ser Gly
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 Gly Pro Pro Gln Pro Ser Ala Phe Ser Glu Ser Phe Pro Ser Ser Val
 530 535 540 545

gct gga tat gga gac att tac ctc aat gct ggt ccc atg ttg ttt agt 3958
 Ala Gly Tyr Gly Asp Ile Tyr Leu Asn Ala Gly Pro Met Leu Phe Ser
 550 555 560

gga gac aag gac cat aga ttt gaa tat agc cat ggt cct att gca gtc 4006
 Gly Asp Lys Asp His Arg Phe Glu Tyr Ser His Gly Pro Ile Ala Val
 565 570 575

ctg gca aac agc agt gac cct tcc acg ggg cca gag agt act cat cct 4054
 Leu Ala Asn Ser Ser Asp Pro Ser Thr Gly Pro Glu Ser Thr His Pro
 580 585 590

ttg cca gca aag atg cac aac tat aac tat ggt ggt aac tta cag gaa 4102
 Leu Pro Ala Lys Met His Asn Tyr Asn Tyr Gly Gly Asn Leu Gln Glu
 595 600 605

aat ccg agt ggc ccc agc ctc atg cat gga cag acc tgg act tct cct 4150
 Asn Pro Ser Gly Pro Ser Leu Met His Gly Gln Thr Trp Thr Ser Pro
 610 615 620 625

gcc caa gga cct gga tat tca caa gga tac agg gga cat att agc aca 4198
 Ala Gln Gly Pro Gly Tyr Ser Gln Gly Tyr Arg Gly His Ile Ser Thr
 630 635 640

65/201

tca act ggc aga ggc aga ggc aga ggg tta cca tac tgagtatctg 4244
 Ser Thr Gly Arg Gly Arg Gly Arg Gly Leu Pro Tyr
 645 650

tttttcctca ggcacatcat ttttatctgg aaagactttt cttagctgcaa ttttaaggcag 4304
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 tttttctttt tacaaagcta cctttagtca aaggtcactg tcagtctttg cacctgcttt 4724
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 aataagaagt atacctcctt ctacatgttt ttgtcttact ga cct ctg ata act 174
 Pro Leu Ile Thr

1

gga aca cat gac tct ggg tct gta gaa agt caa ctg atc aaa ctc atc 222
 Gly Thr His Asp Ser Gly Ser Val Glu Ser Gln Leu Ile Lys Leu Ile
 5 10 15 20

66/201

ctc acc atg cat caa ctg ttc aga ctg gtt ttg gga caa aaa gat ctt 270
 Leu Thr Met His Gln Leu Phe Arg Leu Val Leu Gly Gln Lys Asp Leu
 25 30 35

tca cga gct ggg gac ctc ttc tcc tta gat gac tct gag att gaa gac 318
 Ser Arg Ala Gly Asp Leu Phe Ser Leu Asp Asp Ser Glu Ile Glu Asp
 40 45 50

agc ctt aca gaa gct ttg gag caa att aag ata att agc tca tct tca 366
 Ser Leu Thr Glu Ala Leu Glu Gln Ile Lys Ile Ile Ser Ser Ser Ser
 55 60 65

gat tac caa acc aat aac aat gac cag gca gta gtt gaa atc tgt atc 414
 Asp Tyr Gln Thr Asn Asn Asn Asp Gln Ala Val Val Glu Ile Cys Ile
 70 75 80

aca aga atc aca aca gcc atc aga gag acc gag tcc att gaa aag cat 462
 Thr Arg Ile Thr Thr Ala Ile Arg Glu Thr Glu Ser Ile Glu Lys His
 85 90 95 100

gca aag gcc ctt gtg ggg ctc tgg gac tcc tgc ttg gaa cat aac ctg 510
 Ala Lys Ala Leu Val Gly Leu Trp Asp Ser Cys Leu Glu His Asn Leu
 105 110 115

aga ccc ttt ggg aaa gac gaa gac act cct cat gca aaa atc gca tct 558
 Arg Pro Phe Gly Lys Asp Glu Asp Thr Pro His Ala Lys Ile Ala Ser
 120 125 130

gat atc atg agt tgc att tta cag aat tac aac cga ccc cca gtg atg 606
 Asp Ile Met Ser Cys Ile Leu Gln Asn Tyr Asn Arg Pro Pro Val Met
 135 140 145

gca tta gcc atc ccc att gca gtg aaa ttc ctc cac aga ggc aac aag 654
 Ala Leu Ala Ile Pro Ile Ala Val Lys Phe Leu His Arg Gly Asn Lys
 150 155 160

gaa ctg tgc agg aat atg tct aac tac ctg tct ctg gct gca att acc 702
Glu Leu Cys Arg Asn Met Ser Asn Tyr Leu Ser Leu Ala Ala Ile Thr
165 170 175 180

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Lys Ala Asp Leu Leu Ala Asp His Thr Glu Val Ile Val Lys Ser Ile
185 190 195

ctc caa ggt aac acc atg ttg ttg aga gtg tta cct gct gtg tat gaa 798
Leu Gln Gly Asn Thr Met Leu Leu Arg Val Leu Pro Ala Val Tyr Glu
200 205 210

aag cag cct cag cca att aat aga cac ctg aca gaa ctc ctg gcc ttg 846
Lys Gln Pro Gln Pro Ile Asn Arg His Leu Thr Glu Leu Leu Ala Leu
215 220 225

atg tct cag ctg gaa cag cca gaa cag tac cat cta cta cgg ctt ttg 894
Met Ser Gln Leu Glu Gln Pro Glu Gln Tyr His Leu Leu Arg Leu Leu
230 235 240

cat gta gca gca aag aaa aaa caa ctc gag gta gtt cag aag tgt att 942
His Val Ala Ala Lys Lys Lys Gln Leu Glu Val Val Gln Lys Cys Ile
245 250 255 260

cct ttc cta att ggg cat ttg aag gat tca acc cat aat gac atc atc 990
Pro Phe Leu Ile Gly His Leu Lys Asp Ser Thr His Asn Asp Ile Ile
265 270 275

cta aac atc ctc ata gag ata gca gtc tat gag cca gtg gct ttg aac 1038
Leu Asn Ile Leu Ile Glu Ile Ala Val Tyr Glu Pro Val Ala Leu Asn
280 285 290

agt ttt ctt cca atg ctg aaa gag att ggt gag aga ttc ccc tac ctc 1086
Ser Phe Leu Pro Met Leu Lys Glu Ile Gly Glu Arg Phe Pro Tyr Leu
295 300 305

68/201

act gga cag atg gca agg att tat gga gct gtt ggg cat gtg gat gaa 1134
 Thr Gly Gln Met Ala Arg Ile Tyr Gly Ala Val Gly His Val Asp Glu
 310 315 320

gag aga gcc agg agc tgc ctg aca tac ctg gtg agc caa ctg gcc aac 1182
 Glu Arg Ala Arg Ser Cys Leu Thr Tyr Leu Val Ser Gln Leu Ala Asn
 325 330 335 340

atg gag cat tcg ttt cac cat att ctc ctg ctg gag att aaa agc atc 1230
 Met Glu His Ser Phe His His Ile Leu Leu Leu Glu Ile Lys Ser Ile
 345 350 355

acc gac acc ttc tcc tca atc ttg ggc cct cag agc aga gac atc ttc 1278
 Thr Asp Thr Phe Ser Ser Ile Leu Gly Pro Gln Ser Arg Asp Ile Phe
 360 365 370

cgc atg agc aac agc ttc acc gcc att gct aaa ctc ctt acc cga caa 1326
 Arg Met Ser Asn Ser Phe Thr Ala Ile Ala Lys Leu Leu Thr Arg Gln
 375 380 385

ctg gaa aat acc aag gct gga agt ggc agg aga aaa atc agc act gaa 1374
 Leu Glu Asn Thr Lys Ala Gly Ser Gly Arg Arg Lys Ile Ser Thr Glu
 390 395 400

att gaa ttc cct gag aaa ctg gaa gaa acc aag ctc ata gta act gaa 1422
 Ile Glu Phe Pro Glu Lys Leu Glu Glu Thr Lys Leu Ile Val Thr Glu
 405 410 415 420

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 Asn Glu Asp His Glu Lys Leu Gln Val Lys Ile Gln Ala Phe Glu Asp
 425 430 435

aag ata aat gca ggg agc aat acc cct ggc tct atc aga aga tat agt 1518
 Lys Ile Asn Ala Gly Ser Asn Thr Pro Gly Ser Ile Arg Arg Tyr Ser
 440 445 450

69/201

ctg ggc caa gtt tct aaa gaa gaa aga aaa aac att aga ttt aac agg 1566
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 455 460 465

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 Ser Lys Ser Leu Ala Phe His Thr Met Leu Thr Lys Gly Val Gly Ser
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gat gac ggc gaa gat gaa aac agg gga gac ata cca gcc agc atc tct 1662
 Asp Asp Gly Glu Asp Glu Asn Arg Gly Asp Ile Pro Ala Ser Ile Ser
 485 490 495 500

ctt tca gaa ata gac cca ctt ggc caa gga aat gac aag ctg ccg ttt 1710
 Leu Ser Glu Ile Asp Pro Leu Gly Gln Gly Asn Asp Lys Leu Pro Phe
 505 510 515

aag aca gac act gag aga tca cag ctg ggg gag tct tca gtt tca tac 1758
 Lys Thr Asp Thr Glu Arg Ser Gln Leu Gly Glu Ser Ser Val Ser Tyr
 520 525 530

cca aat att ata cat ata gac tca gag aat ttg tca gaa act gtt aaa 1806
 Pro Asn Ile Ile His Ile Asp Ser Glu Asn Leu Ser Glu Thr Val Lys
 535 540 545

gaa aac tcc cag gaa gaa act cca gag aca act gca agt cct ata gaa 1854
 Glu Asn Ser Gln Glu Glu Thr Pro Glu Thr Thr Ala Ser Pro Ile Glu
 550 555 560

tac caa gat aag ctc tac ttg cac tta aaa aaa aac ctc agc aaa gtg 1902
 Tyr Gln Asp Lys Leu Tyr Leu His Leu Lys Lys Asn Leu Ser Lys Val
 565 570 575 580

aaa gca tat gcc atg gaa att gga aag aag att cca gtc cct gat cag 1950
 Lys Ala Tyr Ala Met Glu Ile Gly Lys Lys Ile Pro Val Pro Asp Gln
 585 590 595

70/201

tgt acc att gaa gac act gtg aga agt tgt gta gca aag ttg ttc ttc 1998
 Cys Thr Ile Glu Asp Thr Val Arg Ser Cys Val Ala Lys Leu Phe Phe
 600 605 610

acc tgc tcc ctg aag ggt cat tac tgc cta tac agt aag tcc agt ttt 2046
 Thr Cys Ser Leu Lys Gly His Tyr Cys Leu Tyr Ser Lys Ser Ser Phe
 615 620 625

att ctc atc agc caa gaa cct cag cca tgg atc cag atc atg ttt cta 2094
 Ile Leu Ile Ser Gln Glu Pro Gln Pro Trp Ile Gln Ile Met Phe Leu
 630 635 640

ttt cag cag agc ctg ttt cct gaa ccc ctg tcc att cag agt cat tct 2142
 Phe Gln Gln Ser Leu Phe Pro Glu Pro Leu Ser Ile Gln Ser His Ser
 645 650 655 660

gtg caa ttc ctc aga gct ctg tgg gag aag acc cag gca ggg ggt gct 2190
 Val Gln Phe Leu Arg Ala Leu Trp Glu Lys Thr Gln Ala Gly Gly Ala
 665 670 675

cac agc ttt gaa act gcc atg atg gag tcc acg ttt cca cag cag aag 2238
 His Ser Phe Glu Thr Ala Met Met Glu Ser Thr Phe Pro Gln Gln Lys
 680 685 690

gat ctg gac cag gta cag ctc cat ctg gaa gaa gtg agg ttc ttt gac 2286
 Asp Leu Asp Gln Val Gln Leu His Leu Glu Glu Val Arg Phe Phe Asp
 695 700 705

gtg ttt ggc ttc agt gaa aca gca gga gca tgg caa tgc ttc atg tgc 2334
 Val Phe Gly Phe Ser Glu Thr Ala Gly Ala Trp Gln Cys Phe Met Cys
 710 715 720

aac aat cct gag aaa gca act gtt gta aat caa gat ggc cag cct ctc 2382
 Asn Asn Pro Glu Lys Ala Thr Val Val Asn Gln Asp Gly Gln Pro Leu
 725 730 735 740

71/201

ata gaa gga aaa ctt aaa gag aag caa gtc aga tgg aag ttc atc aaa 2430
 Ile Glu Gly Lys Leu Lys Glu Lys Gln Val Arg Trp Lys Phe Ile Lys
 745 750 755

agg tgg aaa aca cgc tat ttt aca ctg gct gga aat caa ctt ctg ttt 2478
 Arg Trp Lys Thr Arg Tyr Phe Thr Leu Ala Gly Asn Gln Leu Leu Phe
 760 765 770

caa aaa gga aag tct aaa gat gac cct gac gac tgc cca ata gaa ctc 2526
 Gln Lys Gly Lys Ser Lys Asp Asp Pro Asp Asp Cys Pro Ile Glu Leu
 775 780 785

agc aaa gta cag agt gtg aag gct gtg gcc aag aaa cgc agg gac cgc 2574
 Ser Lys Val Gln Ser Val Lys Ala Val Ala Lys Lys Arg Arg Asp Arg
 790 795 800

tct ctc ccc cgg gct ttc gaa atc ttc aca gac aat aaa acc tat gtc 2622
 Ser Leu Pro Arg Ala Phe Glu Ile Phe Thr Asp Asn Lys Thr Tyr Val
 805 810 815 820

ttt aag gcc aag gat gag aag aat gca gaa gaa tgg ctc cag tgc atc 2670
 Phe Lys Ala Lys Asp Glu Lys Asn Ala Glu Glu Trp Leu Gln Cys Ile
 825 830 835

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 Asn Val Ala Val Ala Gln Ala Lys Glu Arg Glu Ser Arg Glu Val Thr
 840 845 850

aca tat ctg tagggattta taagtcagcc atgacaatta tacaccacag 2767
 Thr Tyr Leu
 855

gcattgtatt atcattgccca atgtcaagaa aaagagctaa atttaccaag ccatgttggt 2827
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 tcttagtaaa tgcatactc taacagcttt agtattgact tcagaatata tctgatgcc 2947

72/201

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gaagggaataa gtcactgata aaagaacttc ttagatatg tcatttaaaa ctgtgagaaa 3067
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tgcacctta gttcttcaaa gttgttcttc taaagtcaca gaagcttttg actatttgc 180
ctttctgccc cttcagactg tacaaaggct gcttaaggca gtgcagcccc ttctcaaagt 240

73/201

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 atagtactgt ttgttaactt ctctatttct ga gct agc cag ctt gat gcc cga 1613

Ala Ser Gln Leu Asp Ala Arg

1

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aaa tct gca gtt gct ggg ttt ttg ctg ctc ctg aag aac ttt aaa gtt 1661
 Lys Ser Ala Val Ala Gly Phe Leu Leu Leu Leu Lys Asn Phe Lys Val

10

15

20

tta ggc agc ctg tca tcc tct cag tgc agt cag tct ctc agt gtc agt 1709
 Leu Gly Ser Leu Ser Ser Ser Gln Cys Ser Gln Ser Leu Ser Val Ser

25

30

35

cag gtt cat gtg gat gtt cac agc cat tac aat tct gtc gcc aat gaa 1757
 Gln Val His Val Asp Val His Ser His Tyr Asn Ser Val Ala Asn Glu

74/201

40	45	50	55	
act ttt tgc ctt gag atc atg gat agt ttg agg aga tgc tta agc cag				1805
Thr Phe Cys Leu Glu Ile Met Asp Ser Leu Arg Arg Cys Leu Ser Gln				
	60	65	70	
caa gct gat gtt cga ctc atg ctt tat gag ggg ttt tat gat gtt ctt				1853
Gln Ala Asp Val Arg Leu Met Leu Tyr Glu Gly Phe Tyr Asp Val Leu				
	75	80	85	
cga agg aac tct cag ctg gct aat tca gtc atg caa act ctg ctc tca				1901
Arg Arg Asn Ser Gln Leu Ala Asn Ser Val Met Gln Thr Leu Leu Ser				
	90	95	100	
cag tta aaa cag ttc tat gag cca aaa cct gat ctg ctg cct cct ctg				1949
Gln Leu Lys Gln Phe Tyr Glu Pro Lys Pro Asp Leu Leu Pro Pro Leu				
	105	110	115	
aaa tta gaa gct tgt att ctg acc caa gga gat aag atc tct cta caa				1997
Lys Leu Glu Ala Cys Ile Leu Thr Gln Gly Asp Lys Ile Ser Leu Gln				
	120	125	130	135
gaa cca ctg gat tat ctg ctg tgt tgt att cag cat tgt ttg gcc tgg				2045
Glu Pro Leu Asp Tyr Leu Leu Cys Cys Ile Gln His Cys Leu Ala Trp				
	140	145	150	
tat aag aat aca gtc ata ccc tta cag cag gga gag gag gaa gag gag				2093
Tyr Lys Asn Thr Val Ile Pro Leu Gln Gln Gly Glu Glu Glu Glu Glu				
	155	160	165	
gag gaa gag gca ttc tac gaa gac cta gat gat ata ttg gag tcc att				2141
Glu Glu Glu Ala Phe Tyr Glu Asp Leu Asp Asp Ile Leu Glu Ser Ile				
	170	175	180	
act aat aga atg att aag agt gag ctg gaa gac ttt gaa ctg gat aaa				2189
Thr Asn Arg Met Ile Lys Ser Glu Leu Glu Asp Phe Glu Leu Asp Lys				

75/201

185	190	195	
tca gca gat ttt tct cag agc acc agt att ggc ata aaa aat aat atc			2237
Ser Ala Asp Phe Ser Gln Ser Thr Ser Ile Gly Ile Lys Asn Asn Ile			
200	205	210	215
tct gct ttt ctt gtg atg gga gtt tgt gag gtt tta ata gaa tac aat			2285
Ser Ala Phe Leu Val Met Gly Val Cys Glu Val Leu Ile Glu Tyr Asn			
	220	225	230
ttc tcc ata agt agt ttc agt aag aat agg ttt gag gac att ctg agc			2333
Phe Ser Ile Ser Ser Phe Ser Lys Asn Arg Phe Glu Asp Ile Leu Ser			
	235	240	245
tta ttt atg tgt tac aaa aaa ctc tct gac att ctt aat gaa aaa gcg			2381
Leu Phe Met Cys Tyr Lys Lys Leu Ser Asp Ile Leu Asn Glu Lys Ala			
	250	255	260
ggt aaa gcc aaa act aaa atg gcc aac aag aca agt gat agt ctt ttg			2429
Gly Lys Ala Lys Thr Lys Met Ala Asn Lys Thr Ser Asp Ser Leu Leu			
	265	270	275
tcc atg aaa ttt gtg tcc agt ctt ctc act gct ctt ttc agg gat agt			2477
Ser Met Lys Phe Val Ser Ser Leu Leu Thr Ala Leu Phe Arg Asp Ser			
	280	285	290
atc caa agc cac caa gaa agc ctt tct gtt ctc agg tcc agc aat gag			2525
Ile Gln Ser His Gln Glu Ser Leu Ser Val Leu Arg Ser Ser Asn Glu			
	300	305	310
ttt atg cgc tat gca gtg aat gta gct ctg cag aaa gta cag cag cta			2573
Phe Met Arg Tyr Ala Val Asn Val Ala Leu Gln Lys Val Gln Gln Leu			
	315	320	325
aag gaa aca ggg cat gtg agt ggc cct gat ggc caa aac cca gaa aag			2621
Lys Glu Thr Gly His Val Ser Gly Pro Asp Gly Gln Asn Pro Glu Lys			

76/201

330	335	340	
atc ttt cag aac ctc tgt gac tta act cga gtc ttg cta tgg aga tac	2669		
Ile Phe Gln Asn Leu Cys Asp Leu Thr Arg Val Leu Leu Trp Arg Tyr			
345	350	355	
act tca att cct act tca gtg gaa gag tcg gga aag aaa gag aaa gga	2717		
Thr Ser Ile Pro Thr Ser Val Glu Glu Ser Gly Lys Lys Glu Lys Gly			
360	365	370	375
aag agc atc tca ctg ctg tgc ttg gag ggt tta cag aaa ata ttc agt	2765		
Lys Ser Ile Ser Leu Leu Cys Leu Glu Gly Leu Gln Lys Ile Phe Ser			
380	385	390	
gct gtg caa cag ttc tat cag ccc aag att cag cag ttt ctc aga gct	2813		
Ala Val Gln Gln Phe Tyr Gln Pro Lys Ile Gln Gln Phe Leu Arg Ala			
395	400	405	
ctg gat gtc aca gat aag gaa gga gaa gag aga gaa gat gca gat gtc	2861		
Leu Asp Val Thr Asp Lys Glu Gly Glu Glu Arg Glu Asp Ala Asp Val			
410	415	420	
agt gtc act cag aga aca gca ttc cag atc cgg caa ttt cag agg tcc	2909		
Ser Val Thr Gln Arg Thr Ala Phe Gln Ile Arg Gln Phe Gln Arg Ser			
425	430	435	
ttg ttg aat tta ctt agc agt caa gag gaa gat ttt aat agc aaa gaa	2957		
Leu Leu Asn Leu Leu Ser Ser Gln Glu Glu Asp Phe Asn Ser Lys Glu			
440	445	450	455
gcc ctc ctg cta gtc acg gtt ctt acc agt ttg tcc aag tta ctg gag	3005		
Ala Leu Leu Leu Val Thr Val Leu Thr Ser Leu Ser Lys Leu Leu Glu			
460	465	470	
ccc tcc tct cct cag ttt gtg cag atg tta tcc tgg aca tca aag att	3053		
Pro Ser Ser Pro Gln Phe Val Gln Met Leu Ser Trp Thr Ser Lys Ile			

77/201

475	480	485	
tgc aag gaa aac agc cgg gag gat gcc ttg ttt tgc aag agc ttg atg			3101
Cys Lys Glu Asn Ser Arg Glu Asp Ala Leu Phe Cys Lys Ser Leu Met			
490	495	500	
aac ttg ctc ttc agc ctg cat gtt tgc tat aag agt cct gtc att ctg			3149
Asn Leu Leu Phe Ser Leu His Val Ser Tyr Lys Ser Pro Val Ile Leu			
505	510	515	
ctg cgt gac ttg tcc cag gat atc cac ggg cat ctg gga gat ata gac			3197
Leu Arg Asp Leu Ser Gln Asp Ile His Gly His Leu Gly Asp Ile Asp			
520	525	530	535
cag gat gta gag gtg gag aaa aca aac cac ttt gca ata gtg aat ttg			3245
Gln Asp Val Glu Val Glu Lys Thr Asn His Phe Ala Ile Val Asn Leu			
540	545	550	
aga acg gct gcc ccc act gtc tgt tta ctt gtt ctg agt cag gcc gag			3293
Arg Thr Ala Ala Pro Thr Val Cys Leu Leu Val Leu Ser Gln Ala Glu			
555	560	565	
aag gtt cta gaa gaa gtg gac tgg cta atc acc aag ctt aag gga caa			3341
Lys Val Leu Glu Glu Val Asp Trp Leu Ile Thr Lys Leu Lys Gly Gln			
570	575	580	
gtg agc caa gaa acc tta tca gaa gag gcc tct tct cag gca acc cta			3389
Val Ser Gln Glu Thr Leu Ser Glu Glu Ala Ser Ser Gln Ala Thr Leu			
585	590	595	
cca aat cag cct gtt gag aaa gct atc atc atg caa ctg gga act ctg			3437
Pro Asn Gln Pro Val Glu Lys Ala Ile Ile Met Gln Leu Gly Thr Leu			
600	605	610	615
ctt aca ttt ttc cac gag ctg gtg cag aca gct ctg cca tca ggc agc			3485
Leu Thr Phe Phe His Glu Leu Val Gln Thr Ala Leu Pro Ser Gly Ser			

78/201

620	625	630	
tgt gtg gac acc ttg tta aag gac ttg tgc aaa atg tac acc aca ctt			3533
Cys Val Asp Thr Leu Leu Lys Asp Leu Cys Lys Met Tyr Thr Thr Leu			
635	640	645	
aca gcc ctt gtc aga tat tat ctc cag gtg tgt cag agc tcc gga gga			3581
Thr Ala Leu Val Arg Tyr Tyr Leu Gln Val Cys Gln Ser Ser Gly Gly			
650	655	660	
att cca aaa aat atg gaa aag ctg gtg aag ctg tct ggt tct cat ctg			3629
Ile Pro Lys Asn Met Glu Lys Leu Val Lys Leu Ser Gly Ser His Leu			
665	670	675	
acc ccc ctg tgt tat tct ttc att tct tac gta cag aat aag agt aag			3677
Thr Pro Leu Cys Tyr Ser Phe Ile Ser Tyr Val Gln Asn Lys Ser Lys			
680	685	690	695
agc ctg aac tat acg gga gag aaa aag gag aaa cct gct gcc gtt gcc			3725
Ser Leu Asn Tyr Thr Gly Glu Lys Lys Glu Lys Pro Ala Ala Val Ala			
700	705	710	
aca gcc atg gcc aga gtt ctt cgg gaa acc aag cca atc cct aac ctc			3773
Thr Ala Met Ala Arg Val Leu Arg Glu Thr Lys Pro Ile Pro Asn Leu			
715	720	725	
atc ttt gcc ata gaa cag tat gaa aaa ttt ctc atc cac ctt tct aag			3821
Ile Phe Ala Ile Glu Gln Tyr Glu Lys Phe Leu Ile His Leu Ser Lys			
730	735	740	
aag tcc aag gtg aac ctg atg cag cac atg aag ctc agc acc tca cga			3869
Lys Ser Lys Val Asn Leu Met Gln His Met Lys Leu Ser Thr Ser Arg			
745	750	755	
gac ttc aag atc aaa gga aac atc cta gac atg gtt ctt cga gag gat			3917
Asp Phe Lys Ile Lys Gly Asn Ile Leu Asp Met Val Leu Arg Glu Asp			

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760

765

770

775

ggc gaa gat gaa aat gaa gag ggc act gca tca gag cat ggg gga cag 3965
 Gly Glu Asp Glu Asn Glu Glu Gly Thr Ala Ser Glu His Gly Gly Gln
 780 785 790

aac aaa gaa cca gcc aag aag aaa agg aaa aaa taaatgaaat gcctgagtta 4018
 Asn Lys Glu Pro Ala Lys Lys Lys Arg Lys Lys
 795 800

atgtgaactt tggggcttct gcttcatttt tacccaacaa gcaacaatgc cccttgctct 4078
 gtagtcacac ccgatgttgg catcttggtt ctgaacccac tgaattcaac tgcaccttca 4138
 gttagaagga atcttcttgg caggtcctgc tactgaaaaa tggctggcct taggcaagcc 4198
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 aaggagctta atgctaaggt caaaaggaga gtgaaaggtt gagaacaatt gccacgaacg 4498
 gtaatgttac atgttaggag ggtctgtttt ctttttatat aagtgtgtct tagatatatt 4558
 ttaaatagaa aataagcttt ctgatttact tgtttggtat ttaaagcaca gtttgttttt 4618
 ctgtcaccta tagagtcaa gaatgcactc tatagaataa attctcttta aac 4671

<210> 13

<211> 4790

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (184)..(2178)

<400> 13

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 tcaccaccag cctgacctca tacactttta gtacaatgga gtggctgagc ctttgagcac 120
 accaccatta catcatcgtg gcaaattaaa gaaggaggtg ggaaaagagg acttattgtt 180

80/201

gtc atg gcc cat gag atg att gga act caa att gtt act gag agg ttg 228
 Met Ala His Glu Met Ile Gly Thr Gln Ile Val Thr Glu Arg Leu
 1 5 10 15

gtg gct ctg ctg gaa agt gga acg gaa aaa gtg ctg cta att gat agc 276
 Val Ala Leu Leu Glu Ser Gly Thr Glu Lys Val Leu Leu Ile Asp Ser
 20 25 30

cgg cca ttt gtg gaa tac aat aca tcc cac att ttg gaa gcc att aat 324
 Arg Pro Phe Val Glu Tyr Asn Thr Ser His Ile Leu Glu Ala Ile Asn
 35 40 45

atc aac tgc tcc aag ctt atg aag cga agg ttg caa cag gac aaa gtg 372
 Ile Asn Cys Ser Lys Leu Met Lys Arg Arg Leu Gln Gln Asp Lys Val
 50 55 60

tta att aca gag ctc atc cag cat tca gcg aaa cat aag gtt gac att 420
 Leu Ile Thr Glu Leu Ile Gln His Ser Ala Lys His Lys Val Asp Ile
 65 70 75

gat tgc agt cag aag gtt gta gtt tac gat caa agc tcc caa gat gtt 468
 Asp Cys Ser Gln Lys Val Val Val Tyr Asp Gln Ser Ser Gln Asp Val
 80 85 90 95

gcc tct ctc tct tca gac tgt ttt ctc act gta ctt ctg ggt aaa ctg 516
 Ala Ser Leu Ser Ser Asp Cys Phe Leu Thr Val Leu Leu Gly Lys Leu
 100 105 110

gag aag agc ttc aac tct gtt cac ctg ctt gca ggt ggg ttt gct gag 564
 Glu Lys Ser Phe Asn Ser Val His Leu Leu Ala Gly Gly Phe Ala Glu
 115 120 125

ttc tct cgt tgt ttc cct ggc ctc tgt gaa gga aaa tcc act cta gtc 612
 Phe Ser Arg Cys Phe Pro Gly Leu Cys Glu Gly Lys Ser Thr Leu Val
 130 135 140

81/201

cct acc tgc att tct cag cct tgc tta cct gtt gcc aac att ggg cca	660
Pro Thr Cys Ile Ser Gln Pro Cys Leu Pro Val Ala Asn Ile Gly Pro	
145 150 155	
acc cga att ctt ccc aat ctt tat ctt ggc tgc cag cga gat gtc ctc	708
Thr Arg Ile Leu Pro Asn Leu Tyr Leu Gly Cys Gln Arg Asp Val Leu	
160 165 170 175	
aac aag gag ctg atg cag cag aat ggg att ggt tat gtg tta aat gcc	756
Asn Lys Glu Leu Met Gln Gln Asn Gly Ile Gly Tyr Val Leu Asn Ala	
180 185 190	
agc aat acc tgt cca aag cct gac ttt atc ccc gag tct cat ttc ctg	804
Ser Asn Thr Cys Pro Lys Pro Asp Phe Ile Pro Glu Ser His Phe Leu	
195 200 205	
cgt gtg cct gtg aat gac agc ttt tgt gag aaa att ttg ccg tgg ttg	852
Arg Val Pro Val Asn Asp Ser Phe Cys Glu Lys Ile Leu Pro Trp Leu	
210 215 220	
gac aaa tca gta gat ttc att gag aaa gca aaa gcc tcc aat gga tgt	900
Asp Lys Ser Val Asp Phe Ile Glu Lys Ala Lys Ala Ser Asn Gly Cys	
225 230 235	
gtt cta gtg cac tgt tta gct ggg atc tcc cgc tcc gcc acc atc gct	948
Val Leu Val His Cys Leu Ala Gly Ile Ser Arg Ser Ala Thr Ile Ala	
240 245 250 255	
atc gcc tac atc atg aag agg atg gac atg tct tta gat gaa gct tac	996
Ile Ala Tyr Ile Met Lys Arg Met Asp Met Ser Leu Asp Glu Ala Tyr	
260 265 270	
aga ttt gtg aaa gaa aaa aga cct act ata tct cca aac ttc aat ttt	1044
Arg Phe Val Lys Glu Lys Arg Pro Thr Ile Ser Pro Asn Phe Asn Phe	
275 280 285	

82/201

ctg ggc caa ctc ctg gac tat gag aag aag att aag aac cag act gga 1092
 Leu Gly Gln Leu Leu Asp Tyr Glu Lys Lys Ile Lys Asn Gln Thr Gly
 290 295 300

gca tca ggg cca aag agc aaa ctc aag ctg ctg cac ctg gag aag cca 1140
 Ala Ser Gly Pro Lys Ser Lys Leu Lys Leu Leu His Leu Glu Lys Pro
 305 310 315

aat gaa cct gtc cct gct gtc tca gag ggt gga cag aaa agc gag acg 1188
 Asn Glu Pro Val Pro Ala Val Ser Glu Gly Gly Gln Lys Ser Glu Thr
 320 325 330 335

ccc ctc agt cca ccc tgt gcc gac tct gct acc tca gag gca gca gga 1236
 Pro Leu Ser Pro Pro Cys Ala Asp Ser Ala Thr Ser Glu Ala Ala Gly
 340 345 350

caa agg ccc gtg cat ccc gcc agc gtg ccc agc gtg ccc agc gtg cag 1284
 Gln Arg Pro Val His Pro Ala Ser Val Pro Ser Val Pro Ser Val Gln
 355 360 365

ccg tcg ctg tta gag gac agc ccg ctg gta cag gcg ctc agt ggg ctg 1332
 Pro Ser Leu Leu Glu Asp Ser Pro Leu Val Gln Ala Leu Ser Gly Leu
 370 375 380

cac ctg tcc gca gac agg ctg gaa gac agc aat aag ctc aag cgt tcc 1380
 His Leu Ser Ala Asp Arg Leu Glu Asp Ser Asn Lys Leu Lys Arg Ser
 385 390 395

ttc tct ctg gat atc aaa tca gtt tca tat tca gcc agc atg gca gca 1428
 Phe Ser Leu Asp Ile Lys Ser Val Ser Tyr Ser Ala Ser Met Ala Ala
 400 405 410 415

tcc tta cat ggc ttc tcc tca tca gaa gat gct ttg gaa tac tac aaa 1476
 Ser Leu His Gly Phe Ser Ser Ser Glu Asp Ala Leu Glu Tyr Tyr Lys
 420 425 430

83/201

cct tcc act act ctg gat ggg acc aac aag cta tgc cag ttc tcc cct 1524
 Pro Ser Thr Thr Leu Asp Gly Thr Asn Lys Leu Cys Gln Phe Ser Pro
 435 440 445

gtt cag gaa cta tcg gag cag act ccc gaa acc agt cct gat aag gag 1572
 Val Gln Glu Leu Ser Glu Gln Thr Pro Glu Thr Ser Pro Asp Lys Glu
 450 455 460

gaa gcc agc atc ccc aag aag ctg cag acc gcc agg cct tca gac agc 1620
 Glu Ala Ser Ile Pro Lys Lys Leu Gln Thr Ala Arg Pro Ser Asp Ser
 465 470 475

cag agc aag cga ttg cat tcg gtc aga acc agc agc agt ggc acc gcc 1668
 Gln Ser Lys Arg Leu His Ser Val Arg Thr Ser Ser Ser Gly Thr Ala
 480 485 490 495

cag agg tcc ctt tta tct cca ctg cat cga agt ggg agc gtg gag gac 1716
 Gln Arg Ser Leu Leu Ser Pro Leu His Arg Ser Gly Ser Val Glu Asp
 500 505 510

aat tac cac acc agc ttc ctt ttc ggc ctt tcc acc agc cag cag cac 1764
 Asn Tyr His Thr Ser Phe Leu Phe Gly Leu Ser Thr Ser Gln Gln His
 515 520 525

ctc acg aag tct gct ggc ctg ggc ctt aag ggc tgg cac tcg gat atc 1812
 Leu Thr Lys Ser Ala Gly Leu Gly Leu Lys Gly Trp His Ser Asp Ile
 530 535 540

ttg gcc ccc cag acc tct acc cct tcc ctg acc agc agc tgg tat ttt 1860
 Leu Ala Pro Gln Thr Ser Thr Pro Ser Leu Thr Ser Ser Trp Tyr Phe
 545 550 555

gcc aca gag tcc tca cac ttc tac tct gcc tca gcc atc tac gga ggc 1908
 Ala Thr Glu Ser Ser His Phe Tyr Ser Ala Ser Ala Ile Tyr Gly Gly
 560 565 570 575

84/201

agt gcc agt tac tct gcc tac agc tgc agc cag ctg ccc act tgc gga 1956
 Ser Ala Ser Tyr Ser Ala Tyr Ser Cys Ser Gln Leu Pro Thr Cys Gly
 580 585 590

gac caa gtc tat tct gtg cgc agg cgg cag aag cca agt gac aga gct 2004
 Asp Gln Val Tyr Ser Val Arg Arg Arg Gln Lys Pro Ser Asp Arg Ala
 595 600 605

gac tcg cgg cgg agc tgg cat gaa gag agc ccc ttt gaa aag cag ttt 2052
 Asp Ser Arg Arg Ser Trp His Glu Glu Ser Pro Phe Glu Lys Gln Phe
 610 615 620

aaa cgc aga agc tgc caa atg gaa ttt gga gag agc atc atg tca gag 2100
 Lys Arg Arg Ser Cys Gln Met Glu Phe Gly Glu Ser Ile Met Ser Glu
 625 630 635

aac agg tca cgg gaa gag ctg ggg aaa gtg ggc agt cag tct agc ttt 2148
 Asn Arg Ser Arg Glu Glu Leu Gly Lys Val Gly Ser Gln Ser Ser Phe
 640 645 650 655

tcg ggc agc atg gaa atc att gag gtc tcc tgagaagaaa gacacttggtg 2198
 Ser Gly Ser Met Glu Ile Ile Glu Val Ser
 660 665

acttctatag acaatttttt tttcttggtc acaaaaaaat tccctgtaaa tctgaaatat 2258
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 gatcaaccca gttgttactc tcttaacatc tgcatttgag agatcagcta atacttctct 2378
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85/201

gctagtcaca cttttcagac caattcaaac tgtctatgca caaaattccc gtgggcctag 2918
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 caacagcagc tttttggggg tggggctggg cgggtgttgt cattgttctt tcccttcctg 3818
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86/201

<211> 4380

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (284)..(1873)

<400> 14

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 ttttactctc tcctttttca taaacagagt cccagattaa tgccagtagt tgattttggg 180
 tctttggggt agtgaagctt gtggatttga cttctctgat tccttttgct gaccttgagt 240
 ggattgtatc tttcactgtt aattataata atttaaaaat tga gtt cta ctt act 295

Val Leu Leu Thr

1

gga cat gaa tct ctg cac ttg aaa gtt aac ata tta aaa gca tat ttt 343
 Gly His Glu Ser Leu His Leu Lys Val Asn Ile Leu Lys Ala Tyr Phe
 5 10 15 20

ttt tct tcc ttg gtt ttc ttg ttc atg tgg ata acc cag aga atg cct 391
 Phe Ser Ser Leu Val Phe Leu Phe Met Trp Ile Thr Gln Arg Met Pro
 25 30 35

gaa tct aag gtg cca tcc tct gag aat cat cgc cca gaa atg tgc tct 439
 Glu Ser Lys Val Pro Ser Ser Glu Asn His Arg Pro Glu Met Cys Ser
 40 45 50

agc tgc aat gtt cct ctt ccc att gga gat agc agc tcc ttc tct ggg 487
 Ser Cys Asn Val Pro Leu Pro Ile Gly Asp Ser Ser Ser Phe Ser Gly
 55 60 65

agt tgt tcc agc agt cca gaa agg ata gtt tct caa act tcc tct gtt 535
 Ser Cys Ser Ser Ser Pro Glu Arg Ile Val Ser Gln Thr Ser Ser Val
 70 75 80

87/201

gag aac cca ttg gag aac cag aaa aat gat caa aat aat tca gat act 583
 Glu Asn Pro Leu Glu Asn Gln Lys Asn Asp Gln Asn Asn Ser Asp Thr
 85 90 95 100

aag atc tct gag aca gag acc ctt aaa tca tca cag aat ttt cag act 631
 Lys Ile Ser Glu Thr Glu Thr Leu Lys Ser Ser Gln Asn Phe Gln Thr
 105 110 115

ctg cct tca tct cca ctt ctg gtc ccc caa gaa tct ttg gcc tct tct 679
 Leu Pro Ser Ser Pro Leu Leu Val Pro Gln Glu Ser Leu Ala Ser Ser
 120 125 130

gag gtc aaa gag aat tta cgt ata gat tct tct tca gct tca cag cat 727
 Glu Val Lys Glu Asn Leu Arg Ile Asp Ser Ser Ser Ala Ser Gln His
 135 140 145

gga cgg gat gcc atc ctc tat ctc cag aca caa gta gct gaa atg tcc 775
 Gly Arg Asp Ala Ile Leu Tyr Leu Gln Thr Gln Val Ala Glu Met Ser
 150 155 160

cga gtg ata cgt gat ctg cag tcc agg agc tgt ttt aga ttt cat cat 823
 Arg Val Ile Arg Asp Leu Gln Ser Arg Ser Cys Phe Arg Phe His His
 165 170 175 180

tct agg cca agt gag aac tcc tca gtt cct tgg gac atc tcc acc tct 871
 Ser Arg Pro Ser Glu Asn Ser Ser Val Pro Trp Asp Ile Ser Thr Ser
 185 190 195

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105

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Thr Ala Lys Asn Met Pro Gly Asp Ser Ala Asp Leu Phe Gly Asp Gly	
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Thr Thr Glu Asp Gly Ser Ala Ala Asn Gly Arg Leu Trp Arg Thr Val	
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Ile Ile Gly Glu Gln Glu His Arg Ile Asp Leu His Met Ile Arg Pro	
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Tyr Met Lys Val Val Thr His Gly Gly Tyr Tyr Gly Glu Gly Leu Asn	
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Ala Ile Ile Val Phe Ala Ala Cys Phe Leu Pro Asp Ser Ser Leu Pro	
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Asp Tyr His Tyr Ile Met Glu Asn Leu Phe Leu Tyr Val Ile Ser Ser	
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Leu Glu Leu Leu Val Ala Glu Asp Tyr Met Ile Val Tyr Leu Asn Gly	
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20

25

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 Lys Ala Tyr Val Ser Thr Ser Arg Leu Phe Val Ser Gly Val Arg Asp
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 Arg Phe Ala Asp Ser Leu Gln Glu Val Val Asn Tyr His Met Ile Leu
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 135 140 145

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acc agg aag tgc ttc cgc cac ctg gca ctg gac tat gtg ctc cag atc 2264
 Thr Arg Lys Cys Phe Arg His Leu Ala Leu Asp Tyr Val Leu Gln Ile
 165 170 175

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 Asn Val Leu Gln Ala Lys Lys Lys Phe Glu Ile Leu Asp Ser Met Leu
 180 185 190

tcc ttc atg cac gcc cag tcc agc ttc ttc cag cag ggc tac agc ctc 2360
 Ser Phe Met His Ala Gln Ser Ser Phe Phe Gln Gln Gly Tyr Ser Leu
 195 200 205 210

ctg cac cag ctg gac ccc tac atg aag aag ctg gca gcc gag ctg gac 2408
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 215 220 225

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 Gln Leu Val Ile Asp Ser Ala Val Glu Lys Arg Glu Met Glu Arg Lys
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 Glu Ser Lys Val Glu Phe Asp Val Asp Ala Pro Ser Gly Val Val Met
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cgg cgc tgg ttc tcc att cag aac agc cag ctg gtc tac cag aag aag 2648
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122/201

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cac ctg gac gat gac gga tta ccg cac ggg ttc tgc aca gtc acc tac 357
 His Leu Asp Asp Asp Gly Leu Pro His Gly Phe Cys Thr Val Thr Tyr
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 Ser Ser Thr Asp Arg Phe Glu Gly Asn Phe Val His Gly Glu Lys Asn
 85 90 95 100

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 Gly Arg Gly Lys Phe Phe Phe Phe Asp Gly Ser Thr Leu Glu Gly Tyr
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 Tyr Val Asp Asp Ala Leu Gln Gly Gln Gly Val Tyr Thr Tyr Glu Asp
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ggg gga gtt ctc cag ggc acg tat gta gac gga gag ctg aac ggt cca 549
 Gly Gly Val Leu Gln Gly Thr Tyr Val Asp Gly Glu Leu Asn Gly Pro
 135 140 145

gcc cag gaa tat gac aca gat ggg aga ctg atc ttc aag ggg cag tat 597
 Ala Gln Glu Tyr Asp Thr Asp Gly Arg Leu Ile Phe Lys Gly Gln Tyr
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aaa gat aac att cgt cat gga gtg tgc tgg ata tat tac cca gat gga 645
 Lys Asp Asn Ile Arg His Gly Val Cys Trp Ile Tyr Tyr Pro Asp Gly
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 Gly Ser Leu Val Gly Glu Val Asn Glu Asp Gly Glu Met Thr Gly Glu
 185 190 195

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 Lys Ile Ala Tyr Val Tyr Pro Asp Glu Arg Thr Ala Leu Tyr Gly Lys
 200 205 210

ttt att gat gga gag atg ata gaa ggc aaa ctg gct acc ctt atg tcc 789
 Phe Ile Asp Gly Glu Met Ile Glu Gly Lys Leu Ala Thr Leu Met Ser
 215 220 225

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Thr Glu Glu Gly Arg Pro His Phe Glu Leu Met Pro Gly Asn Ser Val	
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Leu Pro Asp Pro Tyr Glu Ser Glu Arg Val Tyr Val Ala Glu Ser Leu	
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Glu Glu Thr Val Ile Asp Val Pro Glu Pro Tyr Asn His Val Ser Lys	
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Tyr Cys Ala Ser Leu Gly His Lys Ala Asn His Ser Phe Thr Pro Asn	
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Cys Ile Tyr Asp Met Phe Val His Pro Arg Phe Gly Pro Ile Lys Cys	
360 365 370	

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 Glu Trp Tyr Gln Val Glu Leu Lys Ala Phe Gln Ala Thr Gln Gln Lys
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<221> CDS

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taatctgac tcagaagtgg ctgacgtgg caggatgtgt cgacgatgat ga tgg caa 178
Trp Gln
1

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Glu Ser Lys Met Ser Glu Phe Pro Pro Thr Thr Ser Val Trp Trp Asp
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Tyr Leu Gly Pro Arg Arg Lys Arg Ala Ser Val Gly Leu Glu Ser Leu
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Asp His Thr Ser Val Leu Ser Thr Ser Asp Phe Gly Gly Arg Val Val
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70 75 80

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Asp Cys Val Glu Cys Lys Met His Ile Val Glu Gln Thr Glu Phe Ile
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Gln Met Pro Asp Gly Lys Leu Leu Val Asp Gly Phe Leu Leu Gly Ile
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215 220 225

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Gln Leu Ile Asp Lys Ser Arg Gly Lys Thr Lys Ile Ile Pro Tyr Phe	
245 250 255	
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Glu Ala Leu Lys Gln Gln Ser Gln Gln Ile Ala Thr Ala Lys Asp Lys	
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Leu Ser Val Ser Arg Lys Met Gln Ala Ser Pro Glu Tyr Gln Asp Tyr	
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Val Tyr Leu Glu Gly Thr Gln Lys Ala Lys Lys Leu Phe Leu Gln His	
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Ile His Arg Leu Lys His Glu His Ile Glu Arg Arg Arg Lys Leu Tyr	
325 330 335	
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Glu Ile Asp His Leu Ser Cys Ile Lys Ala Lys Lys Leu Leu Glu Thr	
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 485 490 495

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 565 570 575

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 630 635 640

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 Arg Leu Pro Val Asn Ser Phe Gln Thr Pro Thr Phe Gln Pro His Gly
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 835 840 845 850

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 855 860 865

atg tta cgt gcc ttt ctt tgt gaa gtg cag gat att atc cct att cag 2818
 Met Leu Arg Ala Phe Leu Cys Glu Val Gln Asp Ile Ile Pro Ile Gln
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ctt gta gca ctc act gat ggc gct gta gat gtc ctg gac aat gac tta 2866
 Leu Val Ala Leu Thr Asp Gly Ala Val Asp Val Leu Asp Asn Asp Leu
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 Ser Arg Glu Gln Leu Thr Glu Gly Glu Glu Ile Ala Gln Glu Ile Asp
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 935 940 945

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 Glu Ala Thr His Met Tyr Asp Asn Ala Ala Glu Ala Cys Ser Thr Thr
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 Glu Glu Val Phe Asn Ser Pro Arg Ala Gly Ser Pro Leu Cys Asn Ser
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 Asn Leu Gln Asp Ser Glu Glu Asp Ile Glu Pro Ser Tyr Ser Leu Phe
 980 985 990

cga gaa gac aca tca ctg cct tct ctg tcc aaa gac cat tct aag ctc 3202
 Arg Glu Asp Thr Ser Leu Pro Ser Leu Ser Lys Asp His Ser Lys Leu
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 Ser Met Glu Leu Glu Gly Asn Asp Gly Leu Ser Phe Ile Met Ser Asn
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 Phe Glu Ser Lys Leu Asn Asn Lys Val Pro Pro Pro Val Lys Pro Lys
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 Pro Pro Val His Phe Glu Ile Thr Lys Gly Asp Leu Ser Tyr Leu Asp
 1045 1050 1055

caa ggc cat agg gat gga cag agg aag tct gtg tct tct agc ccc tgg 3394
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 Leu Pro Gln Asp Gly Phe Asp Pro Ser Asp Tyr Ala Glu Pro Met Asp
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Ser Ser Leu Glu Arg Gly Arg Lys Val Ser Ile Val Ser Lys Pro Val	
1140 1145 1150	
ctg tac agg acg aga tgc acc cgg ctg ggg cgg ttt gct agt tac cgg	3682
Leu Tyr Arg Thr Arg Cys Thr Arg Leu Gly Arg Phe Ala Ser Tyr Arg	
1155 1160 1165 1170	
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Thr Ser Phe Ser Val Gly Ser Asp Asp Glu Leu Gly Pro Ile Arg Lys	
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Lys Glu Glu Asp Gln Ala Ser Gln Gly Tyr Lys Gly Asp Asn Ala Val	
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Ile Pro Tyr Glu Thr Asp Glu Asp Pro Arg Arg Arg Asn Ile Leu Arg	
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Ser Leu Arg Arg Asn Thr Lys Lys Pro Lys Pro Lys Pro Arg Pro Ser	
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 Pro Gly Val Ala Ala Glu Trp Ala Leu Ser Phe Arg Val Val
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 Met Ala Gly Tyr Glu Tyr Val Ser Pro Glu Gln Leu Ala Gly Phe Asp
 15 20 25 30

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 Lys Tyr Lys Tyr Ser Ala Val Asp Thr Asn Pro Leu Ser Leu Tyr Val

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Met His Pro Phe Trp Asn Thr Ile Val Lys Val Phe Pro Thr Trp Leu			
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Ala Pro Asn Leu Ile Thr Phe Ser Gly Phe Leu Leu Val Val Phe Asn			
65	70	75	
ttt ctg cta atg gca tac ttt gat cct gac ttt tat gcc tca gca cca			349
Phe Leu Leu Met Ala Tyr Phe Asp Pro Asp Phe Tyr Ala Ser Ala Pro			
80	85	90	
ggt cac aag cac gtg cct gac tgg gtt tgg att gta gtg ggc atc ctc			397
Gly His Lys His Val Pro Asp Trp Val Trp Ile Val Val Gly Ile Leu			
95	100	105	110
aac ttc gta gcc tac act cta gat ggt gtg gac gga aag caa gct cgc			445
Asn Phe Val Ala Tyr Thr Leu Asp Gly Val Asp Gly Lys Gln Ala Arg			
115	120	125	
aga acc aat tct agc act ccc tta ggg gag ctt ttt gat cat ggc ctg			493
Arg Thr Asn Ser Ser Thr Pro Leu Gly Glu Leu Phe Asp His Gly Leu			
130	135	140	
gat agt tgg tca tgt gtt tac ttt gtt gtg act gtt tat tcc atc ttt			541
Asp Ser Trp Ser Cys Val Tyr Phe Val Val Thr Val Tyr Ser Ile Phe			
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Gly Arg Gly Ser Thr Gly Val Ser Val Phe Val Leu Tyr Leu Leu Leu			
160	165	170	
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Trp Val Val Leu Phe Ser Phe Ile Leu Ser His Trp Glu Lys Tyr Asn			

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175	180	185	190	
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Thr Gly Ile Leu Phe Leu Pro Trp Gly Tyr Asp Ile Ser Gln Val Thr				
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Ile Ser Phe Val Tyr Ile Val Thr Ala Val Val Gly Val Glu Ala Trp				
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Tyr Glu Pro Phe Leu Phe Asn Phe Leu Tyr Arg Asp Leu Phe Thr Ala				
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Tyr Glu Ala Met Val Pro Leu Phe Ser Pro Cys Leu Leu Phe Ile Leu				
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Ser Thr Ala Trp Ile Leu Trp Ser Pro Ser Asp Ile Leu Glu Leu His				
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Pro Arg Val Phe Tyr Phe Met Val Gly Thr Ala Phe Ala Asn Ser Thr				
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320

325

330

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 Ser Asp
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149/201

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85

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95

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Lys Lys His Thr Leu Gln His Glu Glu Ile Lys Phe Ile Cys Ser His

100

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Cys Ser Tyr Ile Ser Tyr Thr Lys Gly Glu Phe Gln Arg His Leu Val

115

120

125

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 Ser Asn Glu Gln Glu Lys Val Leu Ser Ala Glu Lys Thr Lys Ser Leu
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 Pro Ser Val Gln Lys Gln Leu Lys Asn Val Lys Trp Val Arg Ser Tyr
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 Asn Pro Phe Pro Tyr Lys Ala Ala Val Cys Phe Ala Glu Ser Gly Arg
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 625 630 635 640

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995

1000

1005

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1015

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<213> Homo sapiens

<220>

<221> CDS

<222> (17)..(2377)

<400> 26

158/201

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Ala Ala Arg Arg Ser Leu Leu Glu Pro Pro Arg Arg Leu Ser Leu Gly

15

20

25

gcg ggc tcc ggt ccg gcc cgc cgc cgc acc cag gac gga ggc tgc atg 148

Ala Gly Ser Gly Pro Ala Arg Arg Arg Thr Gln Asp Gly Gly Cys Met

30

35

40

ccc gag gac cag gcc ggc gca gcc atg gag gag gcg tct ccc tat tcc 196

Pro Glu Asp Gln Ala Gly Ala Ala Met Glu Glu Ala Ser Pro Tyr Ser

45

50

55

60

tta ctt gat atc tgc ttg aat ttc ttg act act cac ctt gag aag ttc 244

Leu Leu Asp Ile Cys Leu Asn Phe Leu Thr Thr His Leu Glu Lys Phe

65

70

75

tgt tca gcc aga caa gat gga aca ttg tgt ctg cag gaa cct gga gta 292

Cys Ser Ala Arg Gln Asp Gly Thr Leu Cys Leu Gln Glu Pro Gly Val

80

85

90

ttc cca cag gag gtg gct gat cga ctg ctt cgg acc atg gct ttt cat 340

Phe Pro Gln Glu Val Ala Asp Arg Leu Leu Arg Thr Met Ala Phe His

95

100

105

ggt cta ttg aat gat gga act gtg ggt att ttt agg ggc aac cag atg 388

Gly Leu Leu Asn Asp Gly Thr Val Gly Ile Phe Arg Gly Asn Gln Met

110

115

120

cgc tta aag cga gcc tgc att cgc aaa gca aag atc tct gct gtt gct 436

Arg Leu Lys Arg Ala Cys Ile Arg Lys Ala Lys Ile Ser Ala Val Ala

125

130

135

140

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ttc cgg aaa gct ttc tgc cac cac aag tta gtg gaa ctt gat gcc aca 484
 Phe Arg Lys Ala Phe Cys His His Lys Leu Val Glu Leu Asp Ala Thr

145

150

155

ggt gtg aat gct gat atc acg att aca gac att atc agt ggg ctt ggc 532
 Gly Val Asn Ala Asp Ile Thr Ile Thr Asp Ile Ile Ser Gly Leu Gly

160

165

170

agt aac aaa tgg atc cag cag aat ctc cag tgc ctg gtg ctg aat tca 580
 Ser Asn Lys Trp Ile Gln Gln Asn Leu Gln Cys Leu Val Leu Asn Ser

175

180

185

tta act ctc tcc ctc gag gat cct tac gag cgc tgc ttc agc cgg ctt 628
 Leu Thr Leu Ser Leu Glu Asp Pro Tyr Glu Arg Cys Phe Ser Arg Leu

190

195

200

tct ggc ctt cga gct tta agc atc acg aat gtt ctc ttt tac aat gaa 676
 Ser Gly Leu Arg Ala Leu Ser Ile Thr Asn Val Leu Phe Tyr Asn Glu

205

210

215

220

gac ctg gct gaa gtt gcc tca ttg cca aga tta gag agc ttg gat att 724
 Asp Leu Ala Glu Val Ala Ser Leu Pro Arg Leu Glu Ser Leu Asp Ile

225

230

235

tct aac acc tca atc aca gac atc act gct cta ctg gcc tgc aaa gac 772
 Ser Asn Thr Ser Ile Thr Asp Ile Thr Ala Leu Leu Ala Cys Lys Asp

240

245

250

cga ctc aag tct cta acc atg cac cac ttg aaa tgt tta aaa atg aca 820
 Arg Leu Lys Ser Leu Thr Met His His Leu Lys Cys Leu Lys Met Thr

255

260

265

act acc cag ata ctg gat gta gtt cgg gaa ctc aaa cat ctg aat cat 868
 Thr Thr Gln Ile Leu Asp Val Val Arg Glu Leu Lys His Leu Asn His

270

275

280

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ctt gat atc tca gat gat aaa cag ttt aca tca gac ata gct ctt cgc 916
 Leu Asp Ile Ser Asp Asp Lys Gln Phe Thr Ser Asp Ile Ala Leu Arg
 285 290 295 300

tta cta gaa caa aaa gac atc cta cct aac ctt gtt tct ctg gat gtt 964
Leu Leu Glu Gln Lys Asp Ile Leu Pro Asn Leu Val Ser Leu Asp Val
305 310 315

tct ggg aga aag cac gtg aca gat aaa gcc gtt gaa gcc ttt ata caa 1012
Ser Gly Arg Lys His Val Thr Asp Lys Ala Val Glu Ala Phe Ile Gln
320 325 330

caa cgt cca agc atg caa ttt gta ggt ttg ctg gct act gat gct ggt 1060
Gln Arg Pro Ser Met Gln Phe Val Gly Leu Leu Ala Thr Asp Ala Gly
335 340 345

tac tct gaa ttc ctc aca ggc gaa gga cat ttg aag gtg tct ggg gaa 1108
Tyr Ser Glu Phe Leu Thr Gly Glu Gly His Leu Lys Val Ser Gly Glu
350 355 360

gcc aat gaa act cag att gca gaa gca ctg aag cgt tac agt gaa cgg 1156
Ala Asn Glu Thr Gln Ile Ala Glu Ala Leu Lys Arg Tyr Ser Glu Arg
365 370 375 380

gca ttc ttt gtt cgg gaa gct cta ttt cat ctt ttt agt ctg act cat 1204
Ala Phe Phe Val Arg Glu Ala Leu Phe His Leu Phe Ser Leu Thr His
385 390 395

gtg atg gaa aaa aca aag cca gaa att tta aag ctt gtg gtt act ggg 1252
Val Met Glu Lys Thr Lys Pro Glu Ile Leu Lys Leu Val Val Thr Gly
400 405 410

atg aga aac cac cct atg aat ttg cca gtg caa ctg gct gca agc gcc 1300
Met Arg Asn His Pro Met Asn Leu Pro Val Gln Leu Ala Ala Ser Ala
415 420 425

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tgt gta ttt aac tta acc aag cag gat ctt gct gca ggg atg cct gtc 1348
 Cys Val Phe Asn Leu Thr Lys Gln Asp Leu Ala Ala Gly Met Pro Val
 430 435 440

cga ctc ctg gct gat gtg acc cat ttg ctg ctc aaa gcc atg gaa cat 1396
 Arg Leu Leu Ala Asp Val Thr His Leu Leu Leu Lys Ala Met Glu His
 445 450 455 460

ttt ccc aat cac cag cag tta cag aag aat tgc ctc ctt tca ctt tgc 1444
 Phe Pro Asn His Gln Gln Leu Gln Lys Asn Cys Leu Leu Ser Leu Cys
 465 470 475

agt gac cgg atc ctt caa gat gtt cca ttt aac agg ttt gaa gca gcc 1492
 Ser Asp Arg Ile Leu Gln Asp Val Pro Phe Asn Arg Phe Glu Ala Ala
 480 485 490

aag ctt gtc atg cag tgg ctt tgc aac cat gag gat caa aac atg caa 1540
 Lys Leu Val Met Gln Trp Leu Cys Asn His Glu Asp Gln Asn Met Gln
 495 500 505

agg atg gca gtt gct atc att tct atc ctg gct gcc aag ctt tct aca 1588
 Arg Met Ala Val Ala Ile Ile Ser Ile Leu Ala Ala Lys Leu Ser Thr
 510 515 520

gaa caa act gca cag ctt ggt act gag ctc ttc att gtc agg caa ctt 1636
 Glu Gln Thr Ala Gln Leu Gly Thr Glu Leu Phe Ile Val Arg Gln Leu
 525 530 535 540

ctt caa ata gtg aag cag aaa acc aat caa aat tca gtg gac act aca 1684
 Leu Gln Ile Val Lys Gln Lys Thr Asn Gln Asn Ser Val Asp Thr Thr
 545 550 555

ttg aaa ttt act ttg agt gca ctt tgg aac ctc aca gat gaa tct cca 1732
 Leu Lys Phe Thr Leu Ser Ala Leu Trp Asn Leu Thr Asp Glu Ser Pro
 560 565 570

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acc act tgt aga cac ttt att gaa aac caa ggg tta gaa ctc ttc atg 1780
 Thr Thr Cys Arg His Phe Ile Glu Asn Gln Gly Leu Glu Leu Phe Met
 575 580 585

agg gtt cta gag tct ttc cca act gag tca tcc att cag cag aaa gtt 1828
 Arg Val Leu Glu Ser Phe Pro Thr Glu Ser Ser Ile Gln Gln Lys Val
 590 595 600

cta gga ctt ttg aac aat ata gct gaa gta caa gaa tta cat tct gaa 1876
 Leu Gly Leu Leu Asn Asn Ile Ala Glu Val Gln Glu Leu His Ser Glu
 605 610 615 620

tta atg tgg aaa gat ttt ata gac cac atc agt agt ctc cta cac agt 1924
 Leu Met Trp Lys Asp Phe Ile Asp His Ile Ser Ser Leu Leu His Ser
 625 630 635

gtg gaa gtg gaa gtc agt tac ttt gca gct gga att att gcc cat tta 1972
 Val Glu Val Glu Val Ser Tyr Phe Ala Ala Gly Ile Ile Ala His Leu
 640 645 650

ata tcc aga ggt gaa caa gct tgg aca ttg agt cgt agc cag agg aat 2020
 Ile Ser Arg Gly Glu Gln Ala Trp Thr Leu Ser Arg Ser Gln Arg Asn
 655 660 665

tct ctg ctg gat gat ttg cat tca gct att ttg aaa tgg cca act cca 2068
 Ser Leu Leu Asp Asp Leu His Ser Ala Ile Leu Lys Trp Pro Thr Pro
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gag tgt gag atg gta gca tac agg tcc ttt aat cca ttt ttc cca tta 2116
 Glu Cys Glu Met Val Ala Tyr Arg Ser Phe Asn Pro Phe Phe Pro Leu
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ctt ggc tgt ttc aca aca cca gga gtt cag cta tgg gca gtt tgg gcc 2164
 Leu Gly Cys Phe Thr Thr Pro Gly Val Gln Leu Trp Ala Val Trp Ala
 705 710 715

163/201

atg caa cat gtc tgc agc aag aat cct tca agg tat tgc agc atg ctg 2212
 Met Gln His Val Cys Ser Lys Asn Pro Ser Arg Tyr Cys Ser Met Leu
 720 725 730

att gaa gaa gga gga ttg cag cat tta tac aac atc aaa gat cat gaa 2260
 Ile Glu Glu Gly Gly Leu Gln His Leu Tyr Asn Ile Lys Asp His Glu
 735 740 745

cat act gat ccc cat gtc caa cag att gct gtg gcc att ctg gat agc 2308
 His Thr Asp Pro His Val Gln Gln Ile Ala Val Ala Ile Leu Asp Ser
 750 755 760

tta gaa aaa cac att gtg cgc cat ggg agg cca cct ccc tgt aaa aaa 2356
 Leu Glu Lys His Ile Val Arg His Gly Arg Pro Pro Pro Cys Lys Lys
 765 770 775 780

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 Gln Pro Gln Ala Arg Leu Asn
 785

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taaaattgcg tatagaatta aggcacagaa ttgtgtgtaa ggtcctgaat ctggctaaaa 5527

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 aacattaagg aaatctaaag gaaatggaat ttgacttttt agagtataat gatgttctag 5827
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 ttgctttcgt gatatatctt atttgcaaac ttctacataa tcaagtttta tgtttaaaac 6307
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<213> Homo sapiens

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<400> 27

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Val Ser Glu Ile Glu Ser Lys Ala Pro Thr Val Glu Ser Gly Thr

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att gcc agc aaa gag aga acg tta tcc tct ggg cag gaa caa gtt gtt 95

Ile Ala Ser Lys Glu Arg Thr Leu Ser Ser Gly Gln Glu Gln Val Val

20

25

30

gaa agt gat aca cta aca att gag tct gga cca ctt gct agt gaa gat 143

Glu Ser Asp Thr Leu Thr Ile Glu Ser Gly Pro Leu Ala Ser Glu Asp

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35	40	45	
aaa cca ctt tcg tgt ggt aca aac tct gga aaa gaa caa gaa ata aat			191
Lys Pro Leu Ser Cys Gly Thr Asn Ser Gly Lys Glu Gln Glu Ile Asn			
50	55	60	
gag act ctg cct atc aca act gta gct cag agt tca gtt cta ctt cat			239
Glu Thr Leu Pro Ile Thr Thr Val Ala Gln Ser Ser Val Leu Leu His			
65	70	75	
cct caa gaa gaa gca gcc agg att aga atg tca gca agg cag aaa cag			287
Pro Gln Glu Glu Ala Ala Arg Ile Arg Met Ser Ala Arg Gln Lys Gln			
80	85	90	95
ata atg gaa ata gaa gag cag aag caa aag caa ttg gaa tta ctt gaa			335
Ile Met Glu Ile Glu Glu Gln Lys Gln Lys Gln Leu Glu Leu Leu Glu			
100	105	110	
caa att gaa cag cag aaa tta aga tta gaa act gac tgc ttc agg gct			383
Gln Ile Glu Gln Gln Lys Leu Arg Leu Glu Thr Asp Cys Phe Arg Ala			
115	120	125	
cag ctg gaa gaa gaa aaa aga aaa aaa act caa ccg act ggg gta gga			431
Gln Leu Glu Glu Glu Lys Arg Lys Lys Thr Gln Pro Thr Gly Val Gly			
130	135	140	
tgc aga aaa tct cat cac tac ata aat cat ttg gtt ggc att gct cca			479
Cys Arg Lys Ser His His Tyr Ile Asn His Leu Val Gly Ile Ala Pro			
145	150	155	
gca tca tgc cct gta att tct gat gaa gat agt cat agg cag atg att			527
Ala Ser Cys Pro Val Ile Ser Asp Glu Asp Ser His Arg Gln Met Ile			
160	165	170	175
cgt aac tat caa cat cag ctt tta caa caa aac agg tta cac agg cag			575
Arg Asn Tyr Gln His Gln Leu Leu Gln Gln Asn Arg Leu His Arg Gln			

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180	185	190	
tct gtt gaa aca gcc agg aaa caa tta ctt gaa tat caa act atg tta			623
Ser Val Glu Thr Ala Arg Lys Gln Leu Leu Glu Tyr Gln Thr Met Leu			
195	200	205	
aaa gga agg tgc cca tgc gtg tca gct cca tca ttg ata act gat tct			671
Lys Gly Arg Cys Pro Ser Val Ser Ala Pro Ser Leu Ile Thr Asp Ser			
210	215	220	
gtt ata tca gtg cca tca tgg aaa tct gag aga ccg act gct ata tca			719
Val Ile Ser Val Pro Ser Trp Lys Ser Glu Arg Pro Thr Ala Ile Ser			
225	230	235	
gag cat tgg gat caa ggt cag aga ctc aag ttg agt cct aac aaa tac			767
Glu His Trp Asp Gln Gly Gln Arg Leu Lys Leu Ser Pro Asn Lys Tyr			
240	245	250	255
caa ccc ata caa cct ata cag acc tcc aaa tta gaa caa gat cat ttt			815
Gln Pro Ile Gln Pro Ile Gln Thr Ser Lys Leu Glu Gln Asp His Phe			
260	265	270	
cag gta gcg aga caa aat cac ttt cca caa aga cag gtg gaa aca aca			863
Gln Val Ala Arg Gln Asn His Phe Pro Gln Arg Gln Val Glu Thr Thr			
275	280	285	
gaa aca tta cgc gct tca gat att tta acc aat caa gct tta gaa tca			911
Glu Thr Leu Arg Ala Ser Asp Ile Leu Thr Asn Gln Ala Leu Glu Ser			
290	295	300	
caa gaa cat cta agg caa ttc tct cag act gaa aca caa cag aga gac			959
Gln Glu His Leu Arg Gln Phe Ser Gln Thr Glu Thr Gln Gln Arg Asp			
305	310	315	
tat aaa ttg gtc ccc aaa gat tct gag aca ctt tca agg gct ttg tca			1007
Tyr Lys Leu Val Pro Lys Asp Ser Glu Thr Leu Ser Arg Ala Leu Ser			

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320	325	330	335	
cat gac agg cag cta ata tca cag gat gct aga aaa ata tct gaa aca				1055
His Asp Arg Gln Leu Ile Ser Gln Asp Ala Arg Lys Ile Ser Glu Thr				
	340	345	350	
ttt ggg gca aca act ttt caa agt tta gaa tcc caa caa ttg ttc tca				1103
Phe Gly Ala Thr Thr Phe Gln Ser Leu Glu Ser Gln Gln Leu Phe Ser				
	355	360	365	
gag aat agt gaa aat ata tct tac cat tta act gaa cct tct tca ttt				1151
Glu Asn Ser Glu Asn Ile Ser Tyr His Leu Thr Glu Pro Ser Ser Phe				
	370	375	380	
gta cca ctg gta cct cag cat tct ttt agt tct ctg cct gtt aaa gtt				1199
Val Pro Leu Val Pro Gln His Ser Phe Ser Ser Leu Pro Val Lys Val				
	385	390	395	
gag tca gga aaa att caa gaa ccc ttt tca gcc atg agc aaa agt aca				1247
Glu Ser Gly Lys Ile Gln Glu Pro Phe Ser Ala Met Ser Lys Ser Thr				
400	405	410	415	
gtt tcc aca agc cat tct ata atc agc caa atg cat gat agg cct ttg				1295
Val Ser Thr Ser His Ser Ile Ile Ser Gln Met His Asp Arg Pro Leu				
	420	425	430	
ctg ccg tca gag aat atc aca gcc cag caa ggt aat atg aag gcc ctc				1343
Leu Pro Ser Glu Asn Ile Thr Ala Gln Gln Gly Asn Met Lys Ala Leu				
	435	440	445	
caa gaa cag tta gac cta cag aag aaa gtt ctt cag gca act cag gaa				1391
Gln Glu Gln Leu Asp Leu Gln Lys Lys Val Leu Gln Ala Thr Gln Glu				
	450	455	460	
gct cag gaa cag ttg ctt ttg tgc aaa cag aaa gaa gtg gaa cag caa				1439
Ala Gln Glu Gln Leu Leu Leu Cys Lys Gln Lys Glu Val Glu Gln Gln				

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465	470	475	
acg ggc ctc tcg gta ttc ctt ccc ttg gta act cca gat tca tct gct	1487		
Thr Gly Leu Ser Val Phe Leu Pro Leu Val Thr Pro Asp Ser Ser Ala			
480	485	490	495
tta ttg cct tct gcc aaa gca gat ttg ggg aga atc cag gaa tct tca	1535		
Leu Leu Pro Ser Ala Lys Ala Asp Leu Gly Arg Ile Gln Glu Ser Ser			
500	505	510	
cca acc aag aat aat att gca gtt tcc tca gac cat cat gtg atc tca	1583		
Pro Thr Lys Asn Asn Ile Ala Val Ser Ser Asp His His Val Ile Ser			
515	520	525	
caa ctt cag gat aag cgt ttg agt ctt tca cag cct atc cta tca cag	1631		
Gln Leu Gln Asp Lys Arg Leu Ser Leu Ser Gln Pro Ile Leu Ser Gln			
530	535	540	
caa aat aat ttt aaa ttt ctc caa gag cag ttg aat att cag aag gat	1679		
Gln Asn Asn Phe Lys Phe Leu Gln Glu Gln Leu Asn Ile Gln Lys Asp			
545	550	555	
agc ctt cag gct agg cga gaa gcc cag gaa gta ttg tat gta cat aaa	1727		
Ser Leu Gln Ala Arg Arg Glu Ala Gln Glu Val Leu Tyr Val His Lys			
560	565	570	575
cag agt gaa ttg gat aga aga gta tgt tcc gaa cag gct gag ccc tct	1775		
Gln Ser Glu Leu Asp Arg Arg Val Cys Ser Glu Gln Ala Glu Pro Ser			
580	585	590	
ttc cca ttt cag gta gct cag cat aca ttt act tca cta cca tct gct	1823		
Phe Pro Phe Gln Val Ala Gln His Thr Phe Thr Ser Leu Pro Ser Ala			
595	600	605	
gat aca aaa tct gga aaa ata cag gag caa cat tca tct aag agc gag	1871		
Asp Thr Lys Ser Gly Lys Ile Gln Glu Gln His Ser Ser Lys Ser Glu			

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610	615	620	
aaa gga ctt gtt tca tgc caa tct gac atc ccc ata tct cag gat ggg			1919
Lys Gly Leu Val Ser Cys Gln Ser Asp Ile Pro Ile Ser Gln Asp Gly			
625	630	635	
tct ttg agt ttc cta cag cag ttc cta cct cta cat gat agt ttg aag			1967
Ser Leu Ser Phe Leu Gln Gln Phe Leu Pro Leu His Asp Ser Leu Lys			
640	645	650	655
ttg ctc caa gaa cag ttg act aaa cag agg gat act ctt cag gct agg			2015
Leu Leu Gln Glu Gln Leu Thr Lys Gln Arg Asp Thr Leu Gln Ala Arg			
660	665	670	
cat gaa gct cag gtg gaa tta ctt tta cat aga caa aga gat ttg ggg			2063
His Glu Ala Gln Val Glu Leu Leu Leu His Arg Gln Arg Asp Leu Gly			
675	680	685	
gac agt aag tct ggg ctg gtg agc tct tca tcc tca cca gtg gtt gtt			2111
Asp Ser Lys Ser Gly Leu Val Ser Ser Ser Ser Ser Pro Val Val Val			
690	695	700	
cag cat tca gtt gct tca caa gct tct gct aaa gct gag cct agg aga			2159
Gln His Ser Val Ala Ser Gln Ala Ser Ala Lys Ala Glu Pro Arg Arg			
705	710	715	
att cag gag ctt tat tta tct gag aag gag aat gta ggt ccc tcc tgt			2207
Ile Gln Glu Leu Tyr Leu Ser Glu Lys Glu Asn Val Gly Pro Ser Cys			
720	725	730	735
cat ttg ata atc cca aca ttt cag gat aag tct ctt agt ttt cca cag			2255
His Leu Ile Ile Pro Thr Phe Gln Asp Lys Ser Leu Ser Phe Pro Gln			
740	745	750	
cat agc ctg gca cag caa gaa aat ttg aca ata ctc caa gaa cag tca			2303
His Ser Leu Ala Gln Gln Glu Asn Leu Thr Ile Leu Gln Glu Gln Ser			

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755	760	765	
caa ata caa agg gta ata ctt ggt gct aaa gaa gga act cag gaa ttt			2351
Gln Ile Gln Arg Val Ile Leu Gly Ala Lys Glu Gly Thr Gln Glu Phe			
770	775	780	
gta cac aca gaa agt gaa ttg gag aaa aga att tct tct gaa cag act			2399
Val His Thr Glu Ser Glu Leu Glu Lys Arg Ile Ser Ser Glu Gln Thr			
785	790	795	
ggc acc tcc tca tcc ctt tcc cag gtg gat gaa tct gag aga ttc cag			2447
Gly Thr Ser Ser Ser Leu Ser Gln Val Asp Glu Ser Glu Arg Phe Gln			
800	805	810	815
gaa tgt ata tca atc aag agt gac agt acc att ccc tta agc cat cct			2495
Glu Cys Ile Ser Ile Lys Ser Asp Ser Thr Ile Pro Leu Ser His Pro			
820	825	830	
aag atc cca aga tgt cag gaa aga ctt ttg aga gtt tca caa cat atg			2543
Lys Ile Pro Arg Cys Gln Glu Arg Leu Leu Arg Val Ser Gln His Met			
835	840	845	
cta cct cta caa gat aat ttg gag gaa cac caa gca tgg cta gac act			2591
Leu Pro Leu Gln Asp Asn Leu Glu Glu His Gln Ala Trp Leu Asp Thr			
850	855	860	
gag aaa gaa gcc ttt cat ttc agc cag aaa acc caa gaa aat aca tct			2639
Glu Lys Glu Ala Phe His Phe Ser Gln Lys Thr Gln Glu Asn Thr Ser			
865	870	875	
tct gaa caa act ggt tca tct tca ttc ata ccc cag ttg gta cag ctt			2687
Ser Glu Gln Thr Gly Ser Ser Ser Phe Ile Pro Gln Leu Val Gln Leu			
880	885	890	895
tca ttt act tcg tta gct tca gct gag tct ggc aca atc ctg gaa cct			2735
Ser Phe Thr Ser Leu Ala Ser Ala Glu Ser Gly Thr Ile Leu Glu Pro			

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900	905	910	
ctt ttt aca gag agt gaa agt aaa att ttt tca agc cac ctt cag atc			2783
Leu Phe Thr Glu Ser Glu Ser Lys Ile Phe Ser Ser His Leu Gln Ile			
915	920	925	
cca caa ttg cag gat agg ctt ttg agg ata tcg caa ctt atc cag cct			2831
Pro Gln Leu Gln Asp Arg Leu Leu Arg Ile Ser Gln Leu Ile Gln Pro			
930	935	940	
caa caa gat aat ttg aag gca ctt caa gaa cag tta gct aca cag aga			2879
Gln Gln Asp Asn Leu Lys Ala Leu Gln Glu Gln Leu Ala Thr Gln Arg			
945	950	955	
gaa gcc atc att cta gct aga caa gaa gct cgg gaa gaa tta ctt tta			2927
Glu Ala Ile Ile Leu Ala Arg Gln Glu Ala Arg Glu Glu Leu Leu Leu			
960	965	970	975
cat cag agt gaa tgg gag gga aga ata tct ccc gag cag gtt gac acc			2975
His Gln Ser Glu Trp Glu Gly Arg Ile Ser Pro Glu Gln Val Asp Thr			
980	985	990	
tct tcc tta ccc cta gta cca cag cat tca ttc gcc tca tta cct ctt			3023
Ser Ser Leu Pro Leu Val Pro Gln His Ser Phe Ala Ser Leu Pro Leu			
995	1000	1005	
aat gaa tct gaa aga aac caa gaa cca tgt tca att aac agt gat aat			3071
Asn Glu Ser Glu Arg Asn Gln Glu Pro Cys Ser Ile Asn Ser Asp Asn			
1010	1015	1020	
ata gta tcc tca ggt cac tca gag ata cca aca ttg cct gat ggg ctg			3119
Ile Val Ser Ser Gly His Ser Glu Ile Pro Thr Leu Pro Asp Gly Leu			
1025	1030	1035	
ttg ggt tta tca cat ctt gtt tta cct caa caa gat aat ttg att gca			3167
Leu Gly Leu Ser His Leu Val Leu Pro Gln Gln Asp Asn Leu Ile Ala			

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1040	1045	1050	1055	
ctt gaa gaa cac ttg cat gca cag aca gat ttc ctt cct tct att gag Leu Glu Glu His Leu His Ala Gln Thr Asp Phe Leu Pro Ser Ile Glu				3215
	1060	1065	1070	
aaa acc cag aaa gaa ttg gtt ttg tca aaa cca tgt aaa ttt gag gaa Lys Thr Gln Lys Glu Leu Val Leu Ser Lys Pro Cys Lys Phe Glu Glu				3263
	1075	1080	1085	
aag gta tct tct gag cat ttt atc cag tct cac cat ggt gat ttg cag Lys Val Ser Ser Glu His Phe Ile Gln Ser His His Gly Asp Leu Gln				3311
	1090	1095	1100	
gca ctt caa cag cag tta gat aca cag aag aaa gcc att cga tct ata Ala Leu Gln Gln Gln Leu Asp Thr Gln Lys Lys Ala Ile Arg Ser Ile				3359
	1105	1110	1115	
cag gaa gtc caa gaa gaa ttg ctt ttg caa aga tta agt gaa ttg gag Gln Glu Val Gln Glu Glu Leu Leu Leu Gln Arg Leu Ser Glu Leu Glu				3407
	1120	1125	1130	1135
aaa agg gta tca tct gaa caa gtt tgc tcc tct tca ttt gta tcc cag Lys Arg Val Ser Ser Glu Gln Val Cys Ser Ser Ser Phe Val Ser Gln				3455
	1140	1145	1150	
gtg cct gtt gct gac tct gaa aga acc cag aag tct ttc cca acc aaa Val Pro Val Ala Asp Ser Glu Arg Thr Gln Lys Ser Phe Pro Thr Lys				3503
	1155	1160	1165	
agt aat gat act ctt ccc tca agt cat cgt gag att cca aga tta cag Ser Asn Asp Thr Leu Pro Ser Ser His Arg Glu Ile Pro Arg Leu Gln				3551
	1170	1175	1180	
gat aga ctt ttg agt tta tca aag cct att ctg cct cag caa gat aat Asp Arg Leu Leu Ser Leu Ser Lys Pro Ile Leu Pro Gln Gln Asp Asn				3599

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1185	1190	1195	
atg aca gca caa ttg gat gca caa agg gaa gtg atg tat tct tat gag			3647
Met Thr Ala Gln Leu Asp Ala Gln Arg Glu Val Met Tyr Ser Tyr Glu			
1200	1205	1210	1215
aaa ccc cag gaa gaa ctg tct tta aac aaa caa aga aag ttg aac aaa			3695
Lys Pro Gln Glu Glu Leu Ser Leu Asn Lys Gln Arg Lys Leu Asn Lys			
1220	1225	1230	
agt gaa tct gct gag cat act atc ccc tct ttg ttt cta ccc aag gaa			3743
Ser Glu Ser Ala Glu His Thr Ile Pro Ser Leu Phe Leu Pro Lys Glu			
1235	1240	1245	
aca gag cat tcg ttt att cca cta cct ttt gca gaa gct aaa cct aaa			3791
Thr Glu His Ser Phe Ile Pro Leu Pro Phe Ala Glu Ala Lys Pro Lys			
1250	1255	1260	
agc act tgt gaa ttg tat tca tcc cag aat gaa cat gca gcc ccc cca			3839
Ser Thr Cys Glu Leu Tyr Ser Ser Gln Asn Glu His Ala Ala Pro Pro			
1265	1270	1275	
agt aat cct gtg atc cca ggg ttt caa gat aga ctt ttg agt ttt tca			3887
Ser Asn Pro Val Ile Pro Gly Phe Gln Asp Arg Leu Leu Ser Phe Ser			
1280	1285	1290	1295
cag tct gtc tta act cag caa gat aac ttg gga ctt cag aaa cag ttg			3935
Gln Ser Val Leu Thr Gln Gln Asp Asn Leu Gly Leu Gln Lys Gln Leu			
1300	1305	1310	
gat cta caa aga gaa gtt ctg cat tat agc cag aaa gcc cag gaa aaa			3983
Asp Leu Gln Arg Glu Val Leu His Tyr Ser Gln Lys Ala Gln Glu Lys			
1315	1320	1325	
ttg ctt gta cag aga caa aca gca ttg cag cag cag ata cag aaa cat			4031
Leu Leu Val Gln Arg Gln Thr Ala Leu Gln Gln Gln Ile Gln Lys His			

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1330	1335	1340	
gaa gag act ttg aag gat ttc ttt aaa gac agt cag ata agt aag ccc			4079
Glu Glu Thr Leu Lys Asp Phe Phe Lys Asp Ser Gln Ile Ser Lys Pro			
1345	1350	1355	
aca gtt gaa aat gat tta aaa acc cag aag atg ggg cag ctc aga gac			4127
Thr Val Glu Asn Asp Leu Lys Thr Gln Lys Met Gly Gln Leu Arg Asp			
1360	1365	1370	1375
tgg ttt cct aat aca caa gac cta gca gga aat gat caa gaa aat att			4175
Trp Phe Pro Asn Thr Gln Asp Leu Ala Gly Asn Asp Gln Glu Asn Ile			
1380	1385	1390	
agg cat gca gat agg aac aac tct gat gat aat cat ttg gct tca gaa			4223
Arg His Ala Asp Arg Asn Asn Ser Asp Asp Asn His Leu Ala Ser Glu			
1395	1400	1405	
gat act agt gcc aag caa agt ggt gag cat ctg gag aaa gat ctg ggg			4271
Asp Thr Ser Ala Lys Gln Ser Gly Glu His Leu Glu Lys Asp Leu Gly			
1410	1415	1420	
aga aga tcc tca aag cca cct gta gca aaa gtc aaa tgt ggt ttg gac			4319
Arg Arg Ser Ser Lys Pro Pro Val Ala Lys Val Lys Cys Gly Leu Asp			
1425	1430	1435	
tta aac cag cat gaa ctt agt gct ata caa gaa gta gag tca cca gca			4367
Leu Asn Gln His Glu Leu Ser Ala Ile Gln Glu Val Glu Ser Pro Ala			
1440	1445	1450	1455
att ggc aga act tct ata cta ggt aaa cca ggt att tat gaa gac aga			4415
Ile Gly Arg Thr Ser Ile Leu Gly Lys Pro Gly Ile Tyr Glu Asp Arg			
1460	1465	1470	
gac ccc ctg cga gtc tca ata agc cga gaa caa agt ttc ttt ggg agc			4463
Asp Pro Leu Arg Val Ser Ile Ser Arg Glu Gln Ser Phe Phe Gly Ser			

76

1475

14 45

cca ctg gcc cat gat ccg ttt agt tt tggg 4 11 11 11 11 11
 Pro Leu Ala His Asp Pro Phe Ser Cu leuGh

1490

1495

aat gtc tgt ggt gat gac tat gat ga agtga 4 60 60 60 60 60 60
 Asn Val Cys Gly Asp Asp Tyr Asp Ga ilu

1505

1510

1515

gtggaattgt atgcacaagg atatgtggac atattttt 4 20 20 20 20 20 20
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Gln	
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ata gcc ttt gat ttt tat ttt ttg cag tgt tcc agt gtt ttc tct caa	105
Ile Ala Phe Asp Phe Tyr Phe Leu Gln Cys Ser Ser Val Phe Ser Gln	
5 10 15	
aac tct gtg ttt gga aca tca agg atg gat tat ccc aaa atg gat tat	153
Asn Ser Val Phe Gly Thr Ser Arg Met Asp Tyr Pro Lys Met Asp Tyr	
20 25 30	
ttt ctg gat gta gag tct gct cac aga ctc ttg gat gtt gag tca gct	201
Phe Leu Asp Val Glu Ser Ala His Arg Leu Leu Asp Val Glu Ser Ala	
35 40 45	
caa aga ttc ttc tac agt caa gga gct caa gct cgc cgg gcg acc ctg	249
Gln Arg Phe Phe Tyr Ser Gln Gly Ala Gln Ala Arg Arg Ala Thr Leu	
50 55 60 65	
ctc ctg cct ccc aca tta atg gcg gca tcc tcg gag gat gat ata gac	297
Leu Leu Pro Pro Thr Leu Met Ala Ala Ser Ser Glu Asp Asp Ile Asp	
70 75 80	
cgg cgg ccc atc cgg aga gtg cgc tcc aag agc gac acg ccg tac ctc	345
Arg Arg Pro Ile Arg Arg Val Arg Ser Lys Ser Asp Thr Pro Tyr Leu	
85 90 95	
gca gag gcc agg atc tcc ttt aac ctg ggg gca gct gag gaa gtg gag	393
Ala Glu Ala Arg Ile Ser Phe Asn Leu Gly Ala Ala Glu Glu Val Glu	
100 105 110	
agg ctg gcg gcg atg cgt tct gac tcc ctc gtc cca ggc acc cac acc	441
Arg Leu Ala Ala Met Arg Ser Asp Ser Leu Val Pro Gly Thr His Thr	
115 120 125	

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cca ccc atc cgc agg aga agt aag ttt gcc aac ctg gga agg att ttc 489
 Pro Pro Ile Arg Arg Arg Ser Lys Phe Ala Asn Leu Gly Arg Ile Phe
 130 135 140 145

aag cct tgg aaa tgg agg aag aag aaa agc gaa aag ttc aaa cac acg 537
 Lys Pro Trp Lys Trp Arg Lys Lys Lys Ser Glu Lys Phe Lys His Thr
 150 155 160

tca gca gcc ctg gaa agg aaa ata tct atg agg caa agc aga gaa gag 585
 Ser Ala Ala Leu Glu Arg Lys Ile Ser Met Arg Gln Ser Arg Glu Glu
 165 170 175

ctg ata aag cga gga gtc ctg aag gaa atc tat gat aaa gat ggg gaa 633
 Leu Ile Lys Arg Gly Val Leu Lys Glu Ile Tyr Asp Lys Asp Gly Glu
 180 185 190

ctc tct ata tcc aat gaa gag gac tcc cta gaa aat ggg cag tcc ctg 681
 Leu Ser Ile Ser Asn Glu Glu Asp Ser Leu Glu Asn Gly Gln Ser Leu
 195 200 205

agc tcc agc cag ctg tct ctg cct gcc ctg tcc gaa atg gag cca gtc 729
 Ser Ser Ser Gln Leu Ser Leu Pro Ala Leu Ser Glu Met Glu Pro Val
 210 215 220 225

cca atg ccc agg gat ccc tgc tca tat gag gtg ctc caa ccg tca gac 777
 Pro Met Pro Arg Asp Pro Cys Ser Tyr Glu Val Leu Gln Pro Ser Asp
 230 235 240

atc atg gat ggg cca gat cct ggc gcc cct gtg aaa ttg cct tgt ctg 825
 Ile Met Asp Gly Pro Asp Pro Gly Ala Pro Val Lys Leu Pro Cys Leu
 245 250 255

cca gtg aaa ctg tcg cct ccg cta cct cca aag aaa gtc atg atc tgt 873
 Pro Val Lys Leu Ser Pro Pro Leu Pro Pro Lys Lys Val Met Ile Cys
 260 265 270

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 Met Pro Val Gly Gly Pro Asp Leu Ser Leu Val Ser Tyr Thr Ala Gln
 275 280 285

aag agt ggc cag cag ggt gtg gcc cag cac cac cac act gtc ctg ccc 969
 Lys Ser Gly Gln Gln Gly Val Ala Gln His His His Thr Val Leu Pro
 290 295 300 305

tcc cag atc cag cac cag ctg cag tac ggc agc cac ggc cag cac ctc 1017
 Ser Gln Ile Gln His Gln Leu Gln Tyr Gly Ser His Gly Gln His Leu
 310 315 320

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 Pro Ser Thr Thr Gly Ser Leu Pro Met His Pro Ser Gly Cys Arg Met
 325 330 335

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 340 345 350

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 Leu His Ser Gly Asp Gly Val Thr Lys Ala Gly Pro Met Gly Leu Pro
 370 375 380 385

gaa ata aga caa gtg cca act gtt gtg att gaa tgt gat gac aat aaa 1257
 Glu Ile Arg Gln Val Pro Thr Val Val Ile Glu Cys Asp Asp Asn Lys
 390 395 400

gaa aat gtg cct cat gag tca gac tac gaa gac tct tct tgc ctg tat 1305
 Glu Asn Val Pro His Glu Ser Asp Tyr Glu Asp Ser Ser Cys Leu Tyr
 405 410 415

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aca aga gaa gag gag gaa gag gag gag gac gaa gac gac gac agc tca 1353
 Thr Arg Glu Glu Glu Glu Glu Glu Asp Glu Asp Asp Asp Ser Ser
 420 425 430

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 Leu Tyr Thr Ser Ser Leu Ala Met Lys Val Cys Arg Lys Asp Ser Leu
 435 440 445

gcc att aaa ctc agc aac agg ccc tcc aag cga gag ctg gaa gaa aag 1449
 Ala Ile Lys Leu Ser Asn Arg Pro Ser Lys Arg Glu Leu Glu Glu Lys
 450 455 460 465

aac atc ctt ccc agg cag acg gat gag gag cgg ctg gag ctg agg caa 1497
 Asn Ile Leu Pro Arg Gln Thr Asp Glu Glu Arg Leu Glu Leu Arg Gln
 470 475 480

cag att ggc acc aag ctc acc agg cgg ctg agc cag agg cca act gca 1545
 Gln Ile Gly Thr Lys Leu Thr Arg Arg Leu Ser Gln Arg Pro Thr Ala
 485 490 495

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 Glu Glu Leu Glu Gln Arg Asn Ile Leu Lys Arg Lys
 500 505

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gtgtaaccac tgagccaggt aggtgtgac tggccactta acaccctga gccttcagat 4351
cctcagttat aaaccaggag tggtagatga ggtggtcact aggtccctc atggccctag 4411
tattctgtgc ttctgtaaat tttcacctg tgccctctag ctgtccctgg tgaccaaca 4471

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tccagaccac cttttcttcc atccgttttc ccacctgaga catcgcaaaa tgggagttcc 4531
 ctccttcttg ttcttgctgt ctgcctcccc atttaactct gctagattaa ttcatactaa 4591
 gatattaatg gctgactagt ttaataggtt ttatcccact gaaatttgca tttgtacaaa 4651
 tgtcactgtc tgggggctcc ctacttcgg gtgttgctgt ctgccccca gtttatctct 4711
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 agaaatttgc att 4784

<210> 29

<211> 4221

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (52)..(1251)

<400> 29

agggcagtc agatgaaaag agtaccaatg aatctgcctc cagctgaata a acc atg 57
 Thr Met
 1

gag agg aaa aac cca tcc aga gag agc ccc aga aga ctc tct gcc aaa 105
 Glu Arg Lys Asn Pro Ser Arg Glu Ser Pro Arg Arg Leu Ser Ala Lys
 5 10 15

gta ggc aaa ggc aca gag atg aag aaa gtg gct cgt cag ctt ggg atg 153
 Val Gly Lys Gly Thr Glu Met Lys Lys Val Ala Arg Gln Leu Gly Met
 20 25 30

gct gct gct gag tca gac aag gac tct ggc ttt tca gat ggg agc tcg 201
 Ala Ala Ala Glu Ser Asp Lys Asp Ser Gly Phe Ser Asp Gly Ser Ser
 35 40 45 50

gaa tgt ctg agc tct gca gag cag atg gag tcc gag gac atg ctg agc 249
 Glu Cys Leu Ser Ser Ala Glu Gln Met Glu Ser Glu Asp Met Leu Ser

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55	60	65	
gcc tta ggc tgg agc aga gaa gac agg ccg agg cag aac tcc aaa act			297
Ala Leu Gly Trp Ser Arg Glu Asp Arg Pro Arg Gln Asn Ser Lys Thr			
70	75	80	
gca aag aat gcc ttc cct acc ctg tct ccc atg gtc gtc atg aag aat			345
Ala Lys Asn Ala Phe Pro Thr Leu Ser Pro Met Val Val Met Lys Asn			
85	90	95	
gtg ctt gtc aaa cag ggc agc agc tca tcc cag ctc cag tcg tgg act			393
Val Leu Val Lys Gln Gly Ser Ser Ser Ser Gln Leu Gln Ser Trp Thr			
100	105	110	
gtc cag ccc tcc ttt gaa gtg atc tca gca cag cca cag ctc tta ttc			441
Val Gln Pro Ser Phe Glu Val Ile Ser Ala Gln Pro Gln Leu Leu Phe			
115	120	125	130
ctt cat cca cct gta cca tct cct gtc agt cca tgt cac act ggt gag			489
Leu His Pro Pro Val Pro Ser Pro Val Ser Pro Cys His Thr Gly Glu			
135	140	145	
aaa aag tcc gac tcc agg aac tac ttg ccc att ctg aat tct tac acc			537
Lys Lys Ser Asp Ser Arg Asn Tyr Leu Pro Ile Leu Asn Ser Tyr Thr			
150	155	160	
aaa ata gcc cca cat cca ggc aaa agg ggc ctt tcc ctt ggc cca gaa			585
Lys Ile Ala Pro His Pro Gly Lys Arg Gly Leu Ser Leu Gly Pro Glu			
165	170	175	
gaa aaa gga aca agt gga gtg cag aag aaa atc tgt act gag aga ctt			633
Glu Lys Gly Thr Ser Gly Val Gln Lys Lys Ile Cys Thr Glu Arg Leu			
180	185	190	
ggg cct agc ttg tct tcc agt gag cca acc aag gct ggt gct gtc cca			681
Gly Pro Ser Leu Ser Ser Ser Glu Pro Thr Lys Ala Gly Ala Val Pro			

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195	200	205	210	
tcc agt ccc tcg acg cca gca cca ccc agc gcc aaa ctt gcc gag gac	729			
Ser Ser Pro Ser Thr Pro Ala Pro Pro Ser Ala Lys Leu Ala Glu Asp				
215	220	225		
tca gct ctg cag ggt gtg ccc tct ctg gtg gca ggt gga agt cca cag	777			
Ser Ala Leu Gln Gly Val Pro Ser Leu Val Ala Gly Gly Ser Pro Gln				
230	235	240		
act ctt cag ccg gta tcc agc agt cac gtg gct aaa gct ccc agt ctg	825			
Thr Leu Gln Pro Val Ser Ser Ser His Val Ala Lys Ala Pro Ser Leu				
245	250	255		
acc ttc gct tcc ccc gcc agt cct gtc tgc gca tca gac agc act ctc	873			
Thr Phe Ala Ser Pro Ala Ser Pro Val Cys Ala Ser Asp Ser Thr Leu				
260	265	270		
cat ggg tta gag agc aac tct ccc ctt tca cca ctg tcc gct aat tat	921			
His Gly Leu Glu Ser Asn Ser Pro Leu Ser Pro Leu Ser Ala Asn Tyr				
275	280	285	290	
agc tca cct tta tgg gct gca gag cac ctc tgc cgc agc cca gat atc	969			
Ser Ser Pro Leu Trp Ala Ala Glu His Leu Cys Arg Ser Pro Asp Ile				
295	300	305		
ttt tca gag cag cgg cag agc aaa cat agg cgc ttt cag aat acc cta	1017			
Phe Ser Glu Gln Arg Gln Ser Lys His Arg Arg Phe Gln Asn Thr Leu				
310	315	320		
gta gtc cta cat aaa tct ggt ttg ctg gag atc act ttg aaa acc aag	1065			
Val Val Leu His Lys Ser Gly Leu Leu Glu Ile Thr Leu Lys Thr Lys				
325	330	335		
gag ttg att cgt cag aat cag gca act cag gta gaa cta gac cag cta	1113			
Glu Leu Ile Arg Gln Asn Gln Ala Thr Gln Val Glu Leu Asp Gln Leu				

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340	345	350	
aag gag caa acc cag ctg ttt ata gaa gcc acc aag agc agg gcc cct	1161		
Lys Glu Gln Thr Gln Leu Phe Ile Glu Ala Thr Lys Ser Arg Ala Pro			
355	360	365	370
cag gct tgg gcc aag ctg cag gca tct tta aca cct ggg tcc agt aat	1209		
Gln Ala Trp Ala Lys Leu Gln Ala Ser Leu Thr Pro Gly Ser Ser Asn			
375	380	385	
aca ggc agt gac cta gaa gca ttc tct gat cac cca gcc ata	1251		
Thr Gly Ser Asp Leu Glu Ala Phe Ser Asp His Pro Ala Ile			
390	395	400	
tagcacagag gcatattttc ctgttacttg agtggttctt ttagctcatt tgctgttacc	1311		
tactcctgtt tcccaaagct tatgtaagag cttttccttc taaacttaaa ctgtgttg	1371		
gttcacttag gaagccacgt gccaatacct ggctgctgtc ttaactcgta gtctgggcac	1431		
aggatacata tgtccccgtc ccaactgagga cctcagtttg ggagtgcct tgagcccctt	1491		
ttccttagcc tgcaggtgct tcaatggatc atggggcaaa gcaggagatg attgtgtggg	1551		
gctcttcctg ctgtcacctc ccatcatccc actctctcac caggatcaag ggtacagtaa	1611		
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tcccacaagg catcgacta gttggcgag acctaaaatt ccctgggcac aggttgacac	1791		
tgggtgtgag cacttaatca ctcaacgctt tgttttctta cacttgaaaa tcaaggga	1851		
gactagtacc atctgactcc tacactttca ttacaagtca gatttttctt aaactagcag	1911		
gcaaaaacag tacttccaaa ttttaaggta tggaatgaat gcagtacatc tggaattgta	1971		
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gtgtaacctg ttttatgtct aaatatctta aggatagttt cagtggttcc tgggatgtag	2151		
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tggcaacaaa gccagaggtg taatgttggg tatatgaagt tcatctcaa atggagacca	2451		
tgaccagagt ttccagatga tacacgttct ttcagcttc attaaatagg caactatgtt	2511		
tctaaatagt aaagtttcaa aatattctct caatttaaaa tttcatcctc ttgaaaatct	2571		

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ttgttcttta caaaattatc ttaataagtt ctatatggtc agcttcatct tccttttttt 2631
 tttttttgag atggagtttc gctcttggtg cccaggcgga gtacaatggt gggatctcgg 2691
 ctactgcaa cctccgcctc ctgggttcaa gtgattctcc tgccacagcc tcccaagtag 2751
 ctgggattac aggtgcctgc caccatgccc agctaatttt tgtattttta gtagaaatgg 2811
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 cgtgtgattt agatatgact gatttagaag tgaacaactt ggtaacatcc ctagactcca 3111
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 gcagagctgc tgttttctga aggtgagaag ccatttttag ctcagagcaa cccttaagag 3891
 aacttttggc agattttgtt ggcattattg aaatatatat agaaaagttg ctgattgcaa 3951
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 attatagtat tgtctgactt tttattttct actatggttc ctttagcaga aaagtaactt 4071
 ttgtgcataat attgaagtgg tttttcagct atgaattctt taggtagaa atttatttag 4131
 caaatgtgaa ttcttttgag aaagtatgaa gttttgcaga aattgactgt gaaatgtcag 4191
 agaaaaataa aagtcactta cttgaaacct 4221

<210> 30

<211> 3776

<212> DNA

<213> Homo sapiens

<220>

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<221> CDS

<222> (232)..(2889)

<400> 30

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gcagggagta ctcatagccg tctgtgcctc ctgctctgct ggactctgat agaggcagtg 120
ggcagcaggg caaagaagga agcagccgcc gaggaagcga aggtggggtg ggggtgcca 180
gccctgcggc cggaggtgcc attgacctg agagcaagag ccatcagtct g atg gct 237
Met Ala

1

tcc tct ggc cgg aag ctg tgg ctg aga tat cct tcc ttc ctc cca gca 285
Ser Ser Gly Arg Lys Leu Trp Leu Arg Tyr Pro Ser Phe Leu Pro Ala
5 10 15

gcc tgg att tgc ctc ctc cca ggc tgg gaa agg cta ggg agg ccc agg 333
Ala Trp Ile Cys Leu Leu Pro Gly Trp Glu Arg Leu Gly Arg Pro Arg
20 25 30

tgg ggc tgt cag ggc caa agg ctg ttt caa aag tgt cct tta ttg cca 381
Trp Gly Cys Gln Gly Gln Arg Leu Phe Gln Lys Cys Pro Leu Leu Pro
35 40 45 50

atc agg ggg ttt ggc tgg cat ctg ctt gtg gca tgg ggt gct ggc tct 429
Ile Arg Gly Phe Gly Trp His Leu Leu Val Ala Trp Gly Ala Gly Ser
55 60 65

cgt gga gca aga ctg agg gct gtc gag ccc cag ggg tcc tgc cca tca 477
Arg Gly Ala Arg Leu Arg Ala Val Glu Pro Gln Gly Ser Cys Pro Ser
70 75 80

gca gcc atg ctt acc cct gca gag ctg gcc acg gta gta cgg cgg ttc 525
Ala Ala Met Leu Thr Pro Ala Glu Leu Ala Thr Val Val Arg Arg Phe
85 90 95

tcc cag acc ggc atc cag gac ttc ctg aca ctg acg ctg acg gag ccc 573

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Ser	Gln	Thr	Gly	Ile	Gln	Asp	Phe	Leu	Thr	Leu	Thr	Leu	Thr	Glu	Pro	
100					105					110						
act ggg ctt ctg tac gtg ggc gcc cga gag gcc ctg ttt gcc ttc agc																621
Thr	Gly	Leu	Leu	Tyr	Val	Gly	Ala	Arg	Glu	Ala	Leu	Phe	Ala	Phe	Ser	
115					120					125					130	
atg gag gcc ctg gag ctg caa gga gcg atc tcc tgg gag gcc ccc gtg																669
Met	Glu	Ala	Leu	Glu	Leu	Gln	Gly	Ala	Ile	Ser	Trp	Glu	Ala	Pro	Val	
					135					140					145	
gag aag aag act gag tgt atc cag aaa ggg aag aac aac cag acc gag																717
Glu	Lys	Lys	Thr	Glu	Cys	Ile	Gln	Lys	Gly	Lys	Asn	Asn	Gln	Thr	Glu	
					150					155					160	
tgc ttc aac ttc atc cgc ttc ctg cag ccc tac aat gcc tcc cac ctg																765
Cys	Phe	Asn	Phe	Ile	Arg	Phe	Leu	Gln	Pro	Tyr	Asn	Ala	Ser	His	Leu	
					165					170					175	
tac gtc tgt ggc acc tac gcc ttc cag ccc aag tgc acc tac gtc aac																813
Tyr	Val	Cys	Gly	Thr	Tyr	Ala	Phe	Gln	Pro	Lys	Cys	Thr	Tyr	Val	Asn	
					180					185					190	
atg ctc acc ttc act ttg gag cat gga gag ttt gaa gat ggg aag ggc																861
Met	Leu	Thr	Phe	Thr	Leu	Glu	His	Gly	Glu	Phe	Glu	Asp	Gly	Lys	Gly	
195					200					205					210	
aag tgt ccc tat gac cca gct aag ggc cat gct ggc ctt ctt gtg gat																909
Lys	Cys	Pro	Tyr	Asp	Pro	Ala	Lys	Gly	His	Ala	Gly	Leu	Leu	Val	Asp	
					215					220					225	
ggg gag ctg tac tcg gcc aca ctc aac aac ttc ctg ggc acg gaa ccc																957
Gly	Glu	Leu	Tyr	Ser	Ala	Thr	Leu	Asn	Asn	Phe	Leu	Gly	Thr	Glu	Pro	
					230					235					240	
att atc ctg cgt aac atg ggg ccc cac cac tcc atg aag aca gag tac																1005

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Ile Ile Leu Arg Asn Met Gly Pro His His Ser Met Lys Thr Glu Tyr
 245 250 255

ctg gcc ttt tgg ctc aac gaa cct cac ttt gta ggc tct gcc tat gta 1053
 Leu Ala Phe Trp Leu Asn Glu Pro His Phe Val Gly Ser Ala Tyr Val
 260 265 270

cct gag agt gtg ggc agc ttc acg ggg gac gac gac aag gtc tac ttc 1101
 Pro Glu Ser Val Gly Ser Phe Thr Gly Asp Asp Asp Lys Val Tyr Phe
 275 280 285 290

ttc ttc agg gag cgg gca gtg gag tcc gac tgc tat gcc gag cag gtg 1149
 Phe Phe Arg Glu Arg Ala Val Glu Ser Asp Cys Tyr Ala Glu Gln Val
 295 300 305

gtg gct cgt gtg gcc cgt gtc tgc aag ggc gat atg ggg ggc gca cgg 1197
 Val Ala Arg Val Ala Arg Val Cys Lys Gly Asp Met Gly Gly Ala Arg
 310 315 320

acc ctg cag agg aag tgg acc acg ttc ctg aag gcg cgg ctg gca tgc 1245
 Thr Leu Gln Arg Lys Trp Thr Thr Phe Leu Lys Ala Arg Leu Ala Cys
 325 330 335

tct gcc cgg aac tgg cag ctc tac ttc aac cag ctg cag gcg atg cac 1293
 Ser Ala Pro Asn Trp Gln Leu Tyr Phe Asn Gln Leu Gln Ala Met His
 340 345 350

acc ctg cag gac acc tcc tgg cac aac acc acc ttc ttt ggg gtt ttt 1341
 Thr Leu Gln Asp Thr Ser Trp His Asn Thr Thr Phe Phe Gly Val Phe
 355 360 365 370

caa gca cag tgg ggt gac atg tac ctg tcg gcc atc tgt gag tac cag 1389
 Gln Ala Gln Trp Gly Asp Met Tyr Leu Ser Ala Ile Cys Glu Tyr Gln
 375 380 385

ttg gaa gag atc cag cgg gtg ttt gag ggc ccc tat aag gag tac cat 1437

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Leu Glu Glu Ile Gln Arg Val Phe Glu Gly Pro Tyr Lys Glu Tyr His
 390 395 40

gag gaa gcc cag aag tgg gac cgc tac act gac cct gta cc agc cct 1485
 Glu Glu Ala Gln Lys Trp Asp Arg Tyr Thr Asp Pro Val Pro Ser Pro
 405 410 415

cgg cct ggc tgc tgc att aac aac tgg cat cgg cgc cac ggc tac acc 1533
 Arg Pro Gly Ser Cys Ile Asn Asn Trp His Arg Arg His Glu Tyr Thr
 420 425 430

agc tcc ctg gag cta ccc gac aac atc ctc aac ttc gtc agc aag cac 1581
 Ser Ser Leu Glu Leu Pro Asp Asn Ile Leu Asn Phe Val Lys Lys His
 435 440 445 450

ccg ctg atg gag gag cag gtg ggg cct cgg tgg agc cgc cc ctg ctc 1629
 Pro Leu Met Glu Glu Gln Val Gly Pro Arg Trp Ser Arg Pro Leu Leu
 455 460 465

gtg aag aag ggc acc aac ttc acc cac ctg gtg gcc gac cgt gtt aca 1677
 Val Lys Lys Gly Thr Asn Phe Thr His Leu Val Ala Asp Ad Val Thr
 470 475 48

gga ctt gat gga gcc acc tat aca gtg ctg ttc att ggc agc gga gac 1725
 Gly Leu Asp Gly Ala Thr Tyr Thr Val Leu Phe Ile Gly Thr Gly Asp
 485 490 495

ggc tgg ctg ctc aag gct gtg agc ctg ggg ccc tgg gtt cc ctg att 1773
 Gly Trp Leu Leu Lys Ala Val Ser Leu Gly Pro Trp Val His Leu Ile
 500 505 510

gag gag ctg cag ctg ttt gac cag gag ccc atg aga agc cgt gtg cta 1821
 Glu Glu Leu Gln Leu Phe Asp Gln Glu Pro Met Arg Ser Leu Val Leu
 515 520 525 530

tct cag agc aag aag ctg ctc ttt gcc ggc tcc cgc tct cc ctg gtg 1869

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Ser Gln Ser Lys Lys Leu Leu Phe Ala Gly Ser Arg Ser Gln Leu Val
 535 540 545

cag ctg ccc gtg gcc gac tgc atg aag tat cgc tcc tgt gca gac tgt 1917
 Gln Leu Pro Val Ala Asp Cys Met Lys Tyr Arg Ser Cys Ala Asp Cys
 550 555 560

gtc ctc gcc cgg gac ccc tat tgc gcc tgg agc gtc aac acc agc cgc 1965
 Val Leu Ala Arg Asp Pro Tyr Cys Ala Trp Ser Val Asn Thr Ser Arg
 565 570 575

tgt gtg gcc gtg ggt ggc cac tct gga tct cta ctg atc cag cat gtg 2013
 Cys Val Ala Val Gly Gly His Ser Gly Ser Leu Leu Ile Gln His Val
 580 585 590

atg acc tcg gac act tca ggc atc tgc aac ctc cgt ggc agt aag aaa 2061
 Met Thr Ser Asp Thr Ser Gly Ile Cys Asn Leu Arg Gly Ser Lys Lys
 595 600 605 610

gtc agg ccc act ccc aaa aac atc acg gtg gtg gcg ggc aca gac ctg 2109
 Val Arg Pro Thr Pro Lys Asn Ile Thr Val Val Ala Gly Thr Asp Leu
 615 620 625

gtg ctg ccc tgc cac ctc tcc tcc aac ttg gcc cat gcc cgc tgg acc 2157
 Val Leu Pro Cys His Leu Ser Ser Asn Leu Ala His Ala Arg Trp Thr
 630 635 640

ttt ggg ggc cgg gac ctg cct gcg gaa cag ccc ggg tcc ttc ctc tac 2205
 Phe Gly Gly Arg Asp Leu Pro Ala Glu Gln Pro Gly Ser Phe Leu Tyr
 645 650 655

gat gcc cgg ctc cag gcc ctg gtt gtg atg gct gcc cag ccc cgc cat 2253
 Asp Ala Arg Leu Gln Ala Leu Val Val Met Ala Ala Gln Pro Arg His
 660 665 670

gcc ggg gcc tac cac tgc ttt tca gag gag cag ggg gcg cgg ctg gct 2301

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Ala Gly Ala Tyr His Cys Phe Ser Glu Glu Gln Gly Ala Arg Leu Ala	
675 680 685 690	
gct gaa ggc tac ctt gtg gct gtc gtg gca ggc ccg tcg gtg acc ttg	2349
Ala Glu Gly Tyr Leu Val Ala Val Val Ala Gly Pro Ser Val Thr Leu	
695 700 705	
gag gct cgg gcc ccc ctg gaa aac ctg ggg ctg gtg tgg ctg gcg gtg	2397
Glu Ala Arg Ala Pro Leu Glu Asn Leu Gly Leu Val Trp Leu Ala Val	
710 715 720	
gtg gcc ctg ggg gct gtg tgc ctg gtg ctg ctg ctg ctg gtg ctg tca	2445
Val Ala Leu Gly Ala Val Cys Leu Val Leu Leu Leu Leu Val Leu Ser	
725 730 735	
ttg cgc cgg cgg ctg cgg gaa gag ctg gag aaa ggg gcc aag gct act	2493
Leu Arg Arg Arg Leu Arg Glu Glu Leu Glu Lys Gly Ala Lys Ala Thr	
740 745 750	
gag agg acc ttg gtg tac ccc ctg gag ctg ccc aag gag ccc acc agt	2541
Glu Arg Thr Leu Val Tyr Pro Leu Glu Leu Pro Lys Glu Pro Thr Ser	
755 760 765 770	
ccc ccc ttc cgg ccc tgt cct gaa cca gat gag aaa ctt tgg gat cct	2589
Pro Pro Phe Arg Pro Cys Pro Glu Pro Asp Glu Lys Leu Trp Asp Pro	
775 780 785	
gtc ggt tac tac tat tca gat ggc tcc ctt aag ata gta cct ggg cat	2637
Val Gly Tyr Tyr Tyr Ser Asp Gly Ser Leu Lys Ile Val Pro Gly His	
790 795 800	
gcc cgg tgc cag ccc ggt ggg ggg ccc cct tcg cca cct cca ggc atc	2685
Ala Arg Cys Gln Pro Gly Gly Gly Pro Pro Ser Pro Pro Pro Gly Ile	
805 810 815	
cca ggc cag cct ctg cct tct cca act cgg ctt cac ctg ggg ggt ggg	2733

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Pro Gly Gln Pro Leu Pro Ser Pro Thr Arg Leu His Leu Gly Gly Gly
 820 825 830

cgg aac tca aat gcc aat ggt tac gtg cgc tta caa cta gga ggg gag 2781
 Arg Asn Ser Asn Ala Asn Gly Tyr Val Arg Leu Gln Leu Gly Gly Glu
 835 840 845 850

gac cgg gga ggg ctc ggg cac ccc ctg cct gag ctc gcg gat gaa ctg 2829
 Asp Arg Gly Gly Leu Gly His Pro Leu Pro Glu Leu Ala Asp Glu Leu
 855 860 865

aga cgc aaa ctg cag caa cgc cag cca ctg ccc gac tcc aac ccc gag 2877
 Arg Arg Lys Leu Gln Gln Arg Gln Pro Leu Pro Asp Ser Asn Pro Glu
 870 875 880

gag tca tca gta tgagggaac cccaccgcg tcggcgggaa gcgtgggagg 2929
 Glu Ser Ser Val
 885

tgtagtcct acttttcac aggcaccagc tacctcaggg acatggcacg ggcacctgct 2989
 ctgtctggga cagatactgc ccagcaccca cccggccatg aggacctgct ctgctcagca 3049
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 gtgggtgggg cctccactt ggccccgggg ttcagtggta tttatactt gccttcttcc 3589
 tgtacagggc tgggaaaggc tgtgtgaggg gagagaagg agagggtggg cctgctgtgg 3649
 acaatggcat actctcttcc agccctagga ggagggtcc taacagtgtg acttattgtg 3709
 tccccgcgta tttatttgtt gtaaattttt gagtattttt atattgacaa ataaaatgga 3769
 gaaaatg 3776

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<211> 3766

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (70)..(2748)

<400> 31

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aggggctga gtt tgc cag ggc cca ctt gac cct gtt tcc cac ctc ccg ccc 111

Val Cys Gln Gly Pro Leu Asp Pro Val Ser His Leu Pro Pro

1

5

10

ccc agg tcc gga ggc ggg ggc ccc cgg ggc gac tcg ggg gcg gac cgc 159

Pro Arg Ser Gly Gly Gly Gly Pro Arg Gly Asp Ser Gly Ala Asp Arg

15

20

25

30

ggg gcg gag ctg ccg ccc gtg agt ccg gcc gag cca cct gag ccc gag 207

Gly Ala Glu Leu Pro Pro Val Ser Pro Ala Glu Pro Pro Glu Pro Glu

35

40

45

ccg cgg gac acc gtc gct cct gct ctc cga atg ctg cgc acc gcg atg 255

Pro Arg Asp Thr Val Ala Pro Ala Leu Arg Met Leu Arg Thr Ala Met

50

55

60

ggc ctg agg agc tgg ctc gcc gcc cca tgg ggc gcg ctg ccg cct cgg 303

Gly Leu Arg Ser Trp Leu Ala Ala Pro Trp Gly Ala Leu Pro Pro Arg

65

70

75

cca ccg ctg ctg ctg ctc ctg ctg ctg ctg ctc ctg ctg cag ccg ccg 351

Pro Pro Leu Leu Leu Leu Leu Leu Leu Leu Leu Leu Leu Leu Gln Pro Pro

80

85

90

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cct ccg acc tgg gcg ctc agc ccc cgg atc agc ctg cct ctg ggc tct 399
 Pro Pro Thr Trp Ala Leu Ser Pro Arg Ile Ser Leu Pro Leu Gly Ser
 95 100 105 110

gaa gag cgg cca ttc ctc aga ttc gaa gct gaa cac atc tcc aac tac 447
 Glu Glu Arg Pro Phe Leu Arg Phe Glu Ala Glu His Ile Ser Asn Tyr
 115 120 125

aca gcc ctt ctg ctg agc agg gat ggc agg acc ctg tac gtg ggt gct 495
 Thr Ala Leu Leu Leu Ser Arg Asp Gly Arg Thr Leu Tyr Val Gly Ala
 130 135 140

cga gag gcc ctc ttt gca ctc agt agc aac ctc agc ttc ctg cca ggc 543
 Arg Glu Ala Leu Phe Ala Leu Ser Ser Asn Leu Ser Phe Leu Pro Gly
 145 150 155

ggg gag tac cag gag ctg ctt tgg ggt gca gac gca gag aag aaa cag 591
 Gly Glu Tyr Gln Glu Leu Leu Trp Gly Ala Asp Ala Glu Lys Lys Gln
 160 165 170

cag tgc agc ttc aag ggc aag gac cca cag cgc gac tgt caa aac tac 639
 Gln Cys Ser Phe Lys Gly Lys Asp Pro Gln Arg Asp Cys Gln Asn Tyr
 175 180 185 190

atc aag atc ctc ctg ccg ctc agc ggc agt cac ctg ttc acc tgt ggc 687
 Ile Lys Ile Leu Leu Pro Leu Ser Gly Ser His Leu Phe Thr Cys Gly
 195 200 205

aca gca gcc ttc agc ccc atg tgt acc tac atc aac atg gag aac ttc 735
 Thr Ala Ala Phe Ser Pro Met Cys Thr Tyr Ile Asn Met Glu Asn Phe
 210 215 220

acc ctg gca agg gac gag aag ggg aat gtc ctc ctg gaa gat ggc aag 783
 Thr Leu Ala Arg Asp Glu Lys Gly Asn Val Leu Leu Glu Asp Gly Lys
 225 230 235

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ggc cgt tgt ccc ttc gac ccg aat ttc aag tcc act gcc ctg gtg gtt	831
Gly Arg Cys Pro Phe Asp Pro Asn Phe Lys Ser Thr Ala Leu Val Val	
240 245 250	
gat ggc gag ctc tac act gga aca gtc agc agc ttc caa ggg aat gac	879
Asp Gly Glu Leu Tyr Thr Gly Thr Val Ser Ser Phe Gln Gly Asn Asp	
255 260 265 270	
ccg gcc atc tgc cgg agc caa agc ctt cgc ccc acc aag acc gag agc	927
Pro Ala Ile Ser Arg Ser Gln Ser Leu Arg Pro Thr Lys Thr Glu Ser	
275 280 285	
tcc ctc aac tgg ctg caa gac cca gct ttt gtg gcc tca gcc tac att	975
Ser Leu Asn Trp Leu Gln Asp Pro Ala Phe Val Ala Ser Ala Tyr Ile	
290 295 300	
cct gag agc ctg ggc agc ttg caa ggc gat gat gac aag atc tac ttt	1023
Pro Glu Ser Leu Gly Ser Leu Gln Gly Asp Asp Asp Lys Ile Tyr Phe	
305 310 315	
ttc ttc agc gag act ggc cag gaa ttt gag ttc ttt gag aac acc att	1071
Phe Phe Ser Glu Thr Gly Gln Glu Phe Glu Phe Phe Glu Asn Thr Ile	
320 325 330	
gtg tcc cgc att gcc cgc atc tgc aag ggc gat gag ggt gga gag cgg	1119
Val Ser Arg Ile Ala Arg Ile Cys Lys Gly Asp Glu Gly Gly Glu Arg	
335 340 345 350	
gtg cta cag cag cgc tgg acc tcc ttc ctc aag gcc cag ctg ctg tgc	1167
Val Leu Gln Gln Arg Trp Thr Ser Phe Leu Lys Ala Gln Leu Leu Cys	
355 360 365	
tca cgg ccc gac gat ggc ttc ccc ttc aac gtg ctg cag gat gtc ttc	1215
Ser Arg Pro Asp Asp Gly Phe Pro Phe Asn Val Leu Gln Asp Val Phe	
370 375 380	

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acg ctg agc ccc agc ccc cag gac tgg cgt gac acc ctt ttc tat ggg 1263
 Thr Leu Ser Pro Ser Pro Gln Asp Trp Arg Asp Thr Leu Phe Tyr Gly
 385 390 395

gtc ttc act tcc cag tgg cac agg gga act aca gaa ggc tct gcc gtc 1311
 Val Phe Thr Ser Gln Trp His Arg Gly Thr Thr Glu Gly Ser Ala Val
 400 405 410

tgt gtc ttc aca atg aag gat gtg cag aga gtc ttc agc ggc ctc tac 1359
 Cys Val Phe Thr Met Lys Asp Val Gln Arg Val Phe Ser Gly Leu Tyr
 415 420 425 430

aag gag gtg aac cgt gag aca cag cag tgg tac acc gtg acc cac ccg 1407
 Lys Glu Val Asn Arg Glu Thr Gln Gln Trp Tyr Thr Val Thr His Pro
 435 440 445

gtg ccc aca ccc cgg cct gga gcg tgc atc acc aac agt gcc cgg gaa 1455
 Val Pro Thr Pro Arg Pro Gly Ala Cys Ile Thr Asn Ser Ala Arg Glu
 450 455 460

agg aag atc aac tca tcc ctg cag ctc cca gac cgc gtg ctg aac ttc 1503
 Arg Lys Ile Asn Ser Ser Leu Gln Leu Pro Asp Arg Val Leu Asn Phe
 465 470 475

ctc aag gac cac ttc ctg atg gac ggg cag gtc cga agc cgc atg ctg 1551
 Leu Lys Asp His Phe Leu Met Asp Gly Gln Val Arg Ser Arg Met Leu
 480 485 490

ctg ctg cag ccc cag gct cgc tac cag cgc gtg gct gta cac cgc gtc 1599
 Leu Leu Gln Pro Gln Ala Arg Tyr Gln Arg Val Ala Val His Arg Val
 495 500 505 510

cct ggc ctg cac cac acc tac gat gtc ctc ttc ctg ggc act ggt gac 1647
 Pro Gly Leu His His Thr Tyr Asp Val Leu Phe Leu Gly Thr Gly Asp
 515 520 525

ggc cgg ctc cac aag gca gtg agc gtg ggc ccc cgg gtg cac atc att 1695
Gly Arg Leu His Lys Ala Val Ser Val Gly Pro Arg Val His Ile Ile
530 535 540

gag gag ctg cag atc ttc tca tcg gga cag ccc gtg cag aat ctg ctc 1743
Glu Glu Leu Gln Ile Phe Ser Ser Gly Gln Pro Val Gln Asn Leu Leu
545 550 555

ctg gac acc cac agg ggg ctg ctg tat gcg gcc tca cac tcg ggc gta 1791
Leu Asp Thr His Arg Gly Leu Leu Tyr Ala Ala Ser His Ser Gly Val
560 565 570

gtc cag gtg ccc atg gcc aac tgc agc ctg tac agg agc tgt ggg gac 1839
Val Gln Val Pro Met Ala Asn Cys Ser Leu Tyr Arg Ser Cys Gly Asp
575 580 585 590

tgc ctc ctc gcc egg gac ccc tac tgt gct tgg agc ggc tcc agc tgc 1887
Cys Leu Leu Ala Arg Asp Pro Tyr Cys Ala Trp Ser Gly Ser Ser Cys
595 600 605

aag cac gtc agc ctc tac cag cct cag ctg gcc acc agg ccg tgg atc 1935
Lys His Val Ser Leu Tyr Gln Pro Gln Leu Ala Thr Arg Pro Trp Ile
610 615 620

cag gac atc gag gga gcc agc gcc aag gac ctt tgc agc gcg tct tcg 1983
Gln Asp Ile Glu Gly Ala Ser Ala Lys Asp Leu Cys Ser Ala Ser Ser
625 630 635

gtt gtg tcc ccg tct ttt gta cca aca ggg gag aag cca tgt gag caa 2031
Val Val Ser Pro Ser Phe Val Pro Thr Gly Glu Lys Pro Cys Glu Gln
640 645 650

gtc cag ttc cag ccc aac aca gtg aac act ttg gcc tgc ccg ctc ctc 2079
Val Gln Phe Gln Pro Asn Thr Val Asn Thr Leu Ala Cys Pro Leu Leu
655 660 665 670

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tcc aac ctg gcg acc cga ctc tgg cta cgc aac ggg gcc ccc gtc aat	2127
Ser Asn Leu Ala Thr Arg Leu Trp Leu Arg Asn Gly Ala Pro Val Asn	
675 680 685	
gcc tcg gcc tcc tgc cac gtg cta ccc act ggg gac ctg ctg ctg gtg	2175
Ala Ser Ala Ser Cys His Val Leu Pro Thr Gly Asp Leu Leu Leu Val	
690 695 700	
ggc acc caa cag ctg ggg gag ttc cag tgc tgg tca cta gag gag ggc	2223
Gly Thr Gln Gln Leu Gly Glu Phe Gln Cys Trp Ser Leu Glu Glu Gly	
705 710 715	
ttc cag cag ctg gta gcc agc tac tgc cca gag gtg gtg gag gac ggg	2271
Phe Gln Gln Leu Val Ala Ser Tyr Cys Pro Glu Val Val Glu Asp Gly	
720 725 730	
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Val Ala Asp Gln Thr Asp Glu Gly Gly Ser Val Pro Val Ile Ile Ser	
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Thr Ser Arg Val Ser Ala Pro Ala Gly Gly Lys Ala Ser Trp Gly Ala	
755 760 765	
gac agg tcc tac tgg aag gag ttc ctg gtg atg tgc acg ctc ttt gtg	2415
Asp Arg Ser Tyr Trp Lys Glu Phe Leu Val Met Cys Thr Leu Phe Val	
770 775 780	
ctg gcc gtg ctg ctc cca gtt tta ttc ttg ctc tac cgg cac cgg aac	2463
Leu Ala Val Leu Leu Pro Val Leu Phe Leu Leu Tyr Arg His Arg Asn	
785 790 795	
agc atg aaa gtc ttc ctg aag cag ggg gaa tgt gcc agc gtg cac ccc	2511
Ser Met Lys Val Phe Leu Lys Gln Gly Glu Cys Ala Ser Val His Pro	
800 805 810	

200/201

aag acc tgc cct gtg gtg ctg ccc cct gag acc cgc cca ctc aac ggc 2559
 Lys Thr Cys Pro Val Val Leu Pro Pro Glu Thr Arg Pro Leu Asn Gly
 815 820 825 830

cta ggg ccc cct agc acc ccg ctc gat cac cga ggg tac cag tcc ctg 2607
 Leu Gly Pro Pro Ser Thr Pro Leu Asp His Arg Gly Tyr Gln Ser Leu
 835 840 845

tca gac agc ccc ccg ggg tcc cga gtc ttc act gag tca gag aag agg 2655
 Ser Asp Ser Pro Pro Gly Ser Arg Val Phe Thr Glu Ser Glu Lys Arg
 850 855 860

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 Pro Leu Ser Ile Gln Asp Ser Phe Val Glu Val Ser Pro Val Cys Pro
 865 870 875

cgg ccc cgg gtc cgc ctt ggc tcg gag atc cgt gac tct gtg gtg 2748
 Arg Pro Arg Val Arg Leu Gly Ser Glu Ile Arg Asp Ser Val Val
 880 885 890

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 aactgcaccc tggctctctc ccagtcctc agttaccct ccatccctca ccttctcca 3648

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ctctaaggga tatcaacact gccagcaca ggggccctga atttatgtg tttttataca 3708
ttttttaata agatgcactt tatgtcattt tttataaag tctgaagaat tactgttt 3766

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/11217

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl ⁷ C12N15/12, C07K14/47 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl ⁷ C12N15/12, C07K14/47 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) SwissProt/PIR/GeneSeq, Genbank/EMBL/DDBJ/GeneSeq		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	T. NAGASE et al., Prediction of the Coding Sequences of Unidentified Human Genes. XIX. The complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins in vitro. DNA Research, 31 December, 2000 (31.12.00), Vol.7, pages 347 to 355	1-5
P, A	WO 01/53453 A2 (Hyseq, Inc.), 26 July, 2001 (26.07.01), (Family: none)	1-5
A	WO 99/63085 A1 (Kyowa Hakko Kogyo Co., Ltd.), 09 December, 1999 (09.12.99), & EP 1085090 A1	1-5
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 18 April, 2002 (18.04.02)		Date of mailing of the international search report 30 April, 2002 (30.04.02)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.		Authorized officer Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/11217

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(See extra sheet.)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
SEQ ID NO:1 in claims 1 to 5

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/11217

Continuation of Box No.II of continuation of first sheet(1)

DNAs containing base sequences relating to SEQ ID NOS:1 to 31 as set forth in claim 1 have no chemical structure in common but merely DNAs originating in human adult whole brain, human tonsil, human adult hippocampus and human fetal whole brain are acquired. It cannot be recognized too that there is any common matter in the functions of these DNAs.

Such being the case, the DNAs as set forth in claim 1 are considered not as relating to a group of inventions so linked as to form a single general inventive concept but as being a group of 31 inventions relating to 31 different proteins.

国際調査報告

国際出願番号 PCT/JP01/11217

A. 発明の属する分野の分類 (国際特許分類 (IPC))
Int. Cl⁷ C12N15/12, C07K14/47

B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))
Int. Cl⁷ C12N15/12, C07K14/47

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で利用した電子データベース (データベースの名称、調査に使用した用語)
SwissProt/PIR/GeneSeq, Genbank/EMBL/DBJ/GeneSeq

C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
PX	T. NAGASE et al., Prediction of the Coding Sequences of Unidentified Human Genes. XIX. The complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins <i>in vitro</i> . DNA RESEARCH December 31, 2000, Vol. 7, p. 347-355	1-5
PA	WO 01/53453 A2 (HYSEQ, INC.) 2001.07.26 ファミリーなし	1-5
A	WO 99/63085 A1 (協和醗酵工業株式会社) 1999.12.09 & EP 1085090 A1	1-5

☐ C欄の続きにも文献が列挙されている。☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリー

「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す)
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願

の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日

18.04.02

国際調査報告の発送日

30.04.02

国際調査機関の名称及びあて先

日本国特許庁 (ISA/JP)

郵便番号 100-8915

東京都千代田区霞が関三丁目4番3号

特許庁審査官 (権限のある職員)

本間 夏子



4N

9637

電話番号 03-3581-1101 内線 3488

第 I 欄 請求の範囲の一部の調査ができないときの意見 (第 1 ページの 2 の続き)

法第 8 条第 3 項 (PCT 17 条 (2) (a)) の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1. ☐ 請求の範囲 _____ は、この国際調査機関が調査をすることを要しない対象に係るものである。つまり、
2. ☐ 請求の範囲 _____ は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、
3. ☐ 請求の範囲 _____ は、従属請求の範囲であって PCT 規則 6.4(a) の第 2 文及び第 3 文の規定に従って記載されていない。

第 II 欄 発明の単一性が欠如しているときの意見 (第 1 ページの 3 の続き)

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

請求の範囲 1 に記載された配列番号 1-31 に係る塩基配列を含む DNA は共通の化学構造を有するものでなく、ヒト成人全脳、ヒト扁桃、ヒト成人海馬、ヒト胎児全脳に由来する DNA を取得しているにすぎなく、その予測されている機能についてもなんら共通性があるとは認められない。

よって、請求の範囲 1 に記載された DNA に関する発明は単一の一般的概念を形成するように連関している一群の発明であるとはいえず、異なった 31 個のタンパク質に関する 31 個の発明からなる群であると認められる。

1. ☐ 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。
2. ☐ 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。
3. ☐ 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったため、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。
4. ☒ 出願人が必要な追加調査手数料を期間内に納付しなかったため、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

請求項 1-5 における配列番号 1 について

追加調査手数料の異議の申立てに関する注意

- ☐ 追加調査手数料の納付と共に出願人から異議申立てがあった。
☐ 追加調査手数料の納付と共に出願人から異議申立てがなかった。